

A novel approach in paediatric drug research: The development of a juvenile pig model for pharmacokinetic/pharmacodynamic studies, using desmopressin as case



Elke Gasthuys¹, Joske Millecam¹, Mathias Devreese¹, An Vermeulen², Pauline De Bruyne³, Johan Vande Walle³, Joris Delanghe⁴, Siska Croubels¹

¹Department of Pharmacology, Toxicology and Biochemistry, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium. ²Department of Bio-analysis, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium. ³Department of Pediatrics and Medical Genetics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium. ⁴Department of Clinical Chemistry, Microbiology and Immunology, Faculty of Medicine and Health Sciences, Ghent University Ghent, Belgium.

1. BACKGROUND

Development of appropriate preclinical juvenile animal models is pivotal for proper conduct of paediatric clinical trials. This was also recognized by the European Medicine Agency (EMA) in the 'Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications'. Traditional animal species such as rodents, dogs and non-human primates are not always appropriate models to study age-related pharmacokinetic (PK), pharmacodynamic (PD) and safety parameters. Therefore, alternative models such as the conventional piglet might offer advantages for paediatric drug development. The adult pig has been demonstrated to be a suitable animal model for adult preclinical studies. However, studies investigating the suitability of a paediatric pig model are still lacking. The aim of this work was to evaluate if the conventional piglet is a suitable juvenile animal model for preclinical paediatric studies of renally excreted and/or acting drugs using desmopressin as case.



Figure 1: Ontogeny of GFR of growing piglets and children.

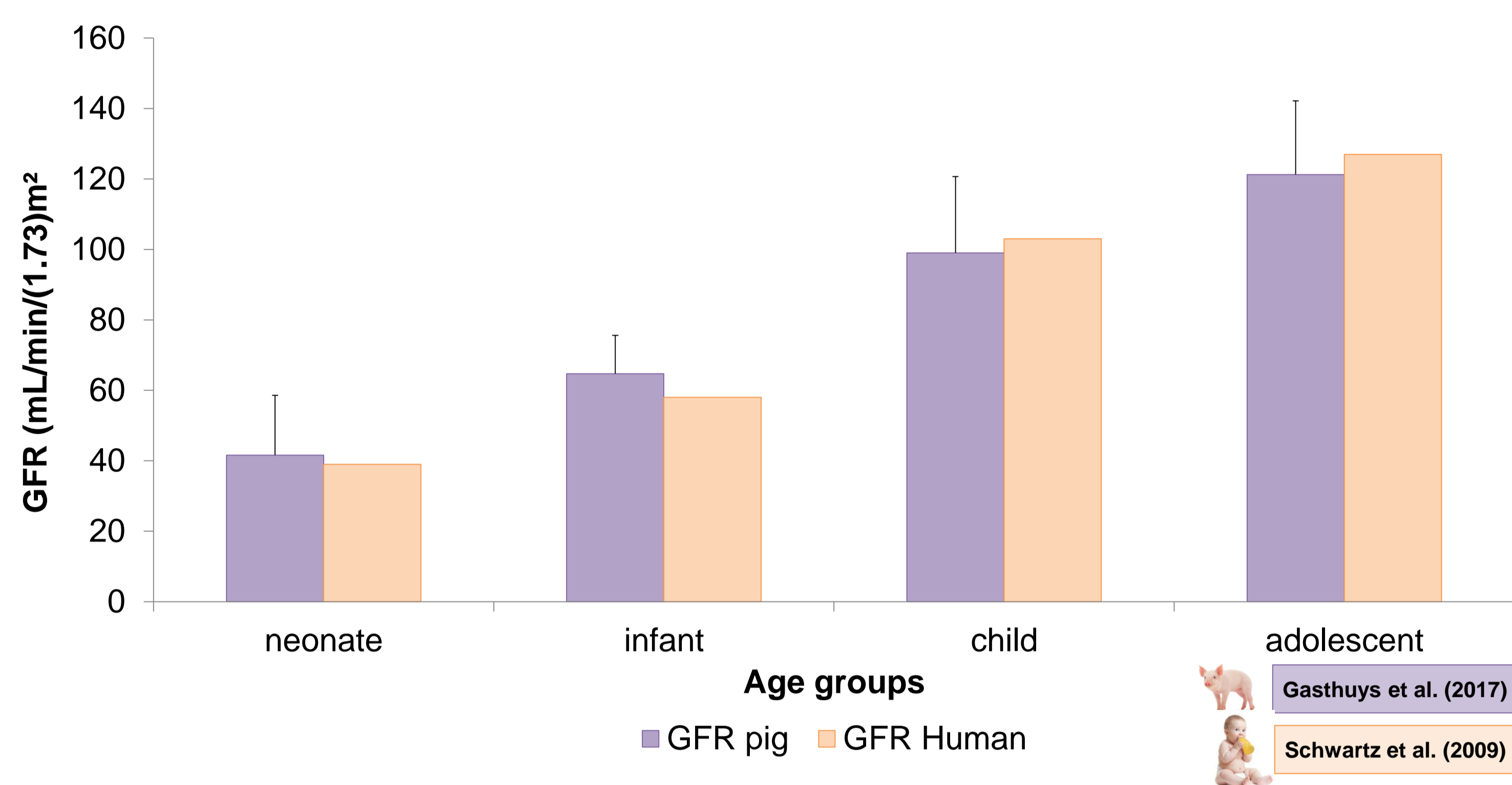
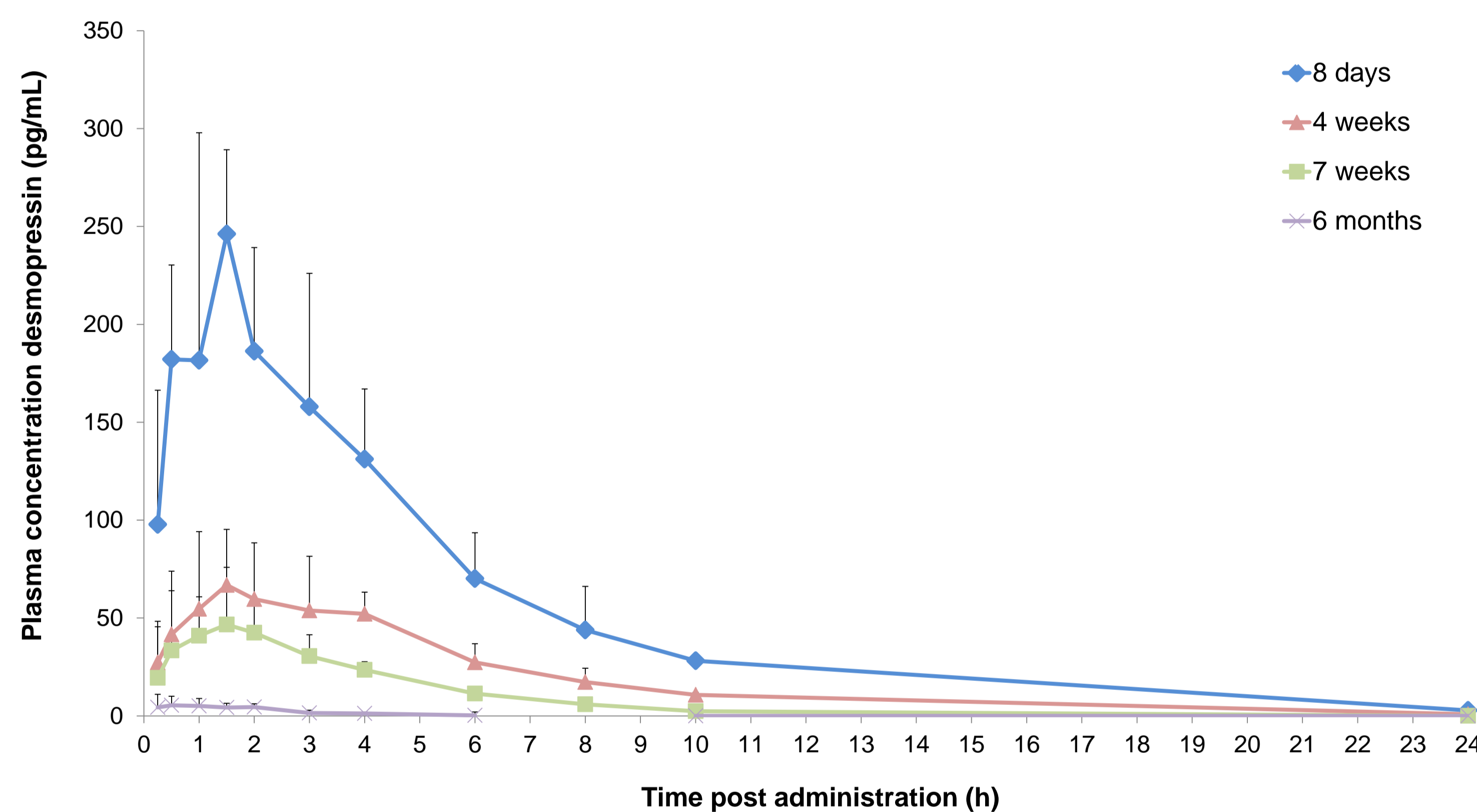


Figure 2: Mean (+SD) desmopressin plasma concentration versus time curves after administration of desmopressin melt (120 µg) to growing piglets aging 8 days, 4/7 weeks and 6 months.



2. METHODS AND RESULTS

Four age categories were included namely, 8-day-old piglets representing neonates, 4-week-old piglets representing infants, 8-week-old piglets representing children and 6-month-old pigs representing adolescents (**Table**). First, blood and urine collection techniques were optimized in the four age categories. Catheterization of the jugular vein was preferred since this is a more ethical method of collecting blood samples in growing piglets. A non-invasive urine collection technique in male piglets was developed using urine collection bags. Next, the ontogeny of the glomerular filtration rate was determined using two different markers, namely creatinine (Jaffe and enzymatic assay) and exo-iohexol (compartmental PK), which was comparable to humans (**Figure 1**). Finally, a PK/PD study with desmopressin was performed in the four age categories. No PD effects were observed between the control and desmopressin-treated groups. Desmopressin plasma concentration-time curves (**Figure 2**) best fitted a two-compartmental model, with dual, sequential first-order absorption, and first-order elimination. Body weight was the only significant covariate on clearance and on volume of distribution of the central compartment. Based on these PK parameters, it is recommended to adapt the human sampling protocol in order to further validate if the pig is a reliable translational model as no double absorption peak was observed in the human paediatric trials.



Neonate	0-1 months	0-2 weeks
Infant	1-24 months	2-4 weeks
Child	2-12 years	4-14 weeks
Adolescent	12-16 years	4-6 months

3. CONCLUSION

This work demonstrates the usefulness of growing conventional piglets to study renally excreted drugs. To establish the added value of the conventional pig among the more traditional animal models, extensive research has to be performed to unravel the ontogeny of other ADME processes and to correlate and extrapolate this with humans

ACKNOWLEDGEMENTS

The SAFE-PEDRUG project (IWT-SBO 130033) is supported by the Agency for Innovation by Science and Technology in Flanders (IWT).

REFERENCES

- Gasthuys et al. Front Pharmacol. 2017 Jun 29;8:431. doi: 10.3389/fphar.2017.00431.
Gasthuys et al. Front Pharmacol. 2018 Jan 31;9:41. doi: 10.3389/fphar.2018.00041.
Schwartz et al. J Am Soc Nephrol. 2009 Mar;20(3):629-37. doi: 10.1681/ASN.2008030287.

