INTRODUCTION
In recent years, an increased interest in research into paediatric drug development has highlighted the important role played by physiologically based pharmacokinetic (PBPK) models in conjunction with other biopharmaceutical tools such as in vitro tests. Such technology supports development of age-appropriate medicines and helps to ensure that development of paediatric medicines is supported by the tools already available for adult medicines [1]. However, there are many gaps in our knowledge of age-specific changes in gastrointestinal (GI) physiology and a lack of published examples leads to uncertainty on the reliability of PBPK-based predictions of oral drug exposure for the paediatric population (newborns: 0-28 days, infants: 1-23 months, children: 2-12 years). By developing and validating paediatric PBPK models for oral drugs we enrich our knowledge of which extrinsic (drug, food and formulation) or intrinsic (GI physiology) variables are influential and uncover the limitations in our ability to predict [1][2][3].

Goal
The aim of this work is to identify age-specific differences and knowledge gaps in the GI anatomy and physiology that give rise to differences in absorption in the paediatric population compared to adults. A secondary goal is to increase the understanding in the anatomy and physiology of the GI tract in paediatric populations using physiologically based pharmacokinetic (PBPK) modelling, parameter sensitivity analysis (PSA) and in vitro dissolution testing. A further goal in this study is to improve the prediction of drug release and absorption in paediatric patients by optimizing PBPK modelling relevant to paediatric age groups.

Method
A systematic literature research was done to collect the current knowledge regarding: GI pH, volume of GI fluid, bile acids, enzymes, GI surface morphology, GI transit time and permeability. The experimental part in this study was carried out using software GastroPlus (G*). This study was restricted to BCS 1 class compounds. Moreover, the drug products have to be available as an immediate release formulation. An in vitro dissolution testing was carried out using software GastroPlus (G*). The analysis may help to increase the understanding of the age-related differences and knowledge gaps in the GI anatomy and physiology that give rise to differences in absorption in the paediatric population compared to adults. The resulted paediatric PBPK models were evaluated using clinical PK data. Evaluating compounds with more complex physico-chemical properties (e.g., poorly water soluble APIs, weak acids/bases) may further improve the accuracy of the model.

RESULTS
The prediction of oral absorption of BCS 1 compounds using PBPK modelling is accurate in adults (C<sub>ratio (obs/pred) 0.86-1.31, AUC<sub>ratio (obs/pred) 0.83-1.05) and 2-12 years old children (C<sub>ratio (obs/pred) 0.78-1.34, AUC<sub>ratio (obs/pred) 0.94-1.50 and t<sub>max ratio (obs/pred) 0.92-1.43) over a various dose range (Fig. 2). However, a poor prediction was obtained in newborn and infants (0-2 years), as can be seen in Fig. 3 (red line) (C<sub>ratio (obs/pred) 0.5-1.49, AUC<sub>ratio (obs/pred) 0.82-1.64 and t<sub>max ratio (obs/pred) 0.13-5.40).

CONCLUSION
There exist significant knowledge gaps in paediatric GI physiology and anatomy. Furthermore, the use of PBPK modelling together with in vitro dissolution testing is an effective strategy for characterizing the anatomical and physiological GI parameters that affect oral drug absorption. The prediction of oral absorption of BCS 1 compounds using PBPK modelling is accurate in adults and 2-12 years old children. However, a poor prediction was obtained in newborn and infants (0-2 years). Including the prolonged GET improved the accuracy of the model. PBPK models simulating the paediatric population need to be further optimized and validated. Evaluating compounds with more complex physico-chemical properties (e.g., poorly water soluble APIs, weak acids/bases) may further improve the understanding of the physiological parameters affecting oral absorption in children.

Reference
[1] Batchelor et al. (2013)