**Physiologically-based pharmacokinetics modelling of Semaglutide in children and adolescents with healthy and obese body weights**

**Pharmacokinetics of Semaglutide in children**

**Thayná Rocco Machado1, Thiago Honorio1, Thaisa F. Souza Domingos2, Dailane da Silva Candido de Paula1, Lucio Mendes Cabral1, Carlos R. Rodrigues1, Bárbara A. Abrahim-Vieira1\*, Alessandra Mendonça Teles de Souza1\***

**1** Laboratory of Molecular Modeling & QSAR (ModMolQSAR), Faculty of Pharmacy, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

**2** BIODATA Computing Services & Consulting, Rio de Janeiro, Brazil

\*Corresponding authors:

Dr. Alessandra Mendonça Teles de Souza &

Dr. Barbara A. Abrahim-Vieira

ModMolQSAR, Av. Carlos Chagas Filho, 373 bloco L subsolo, Cidade Universitária, Rio de Janeiro, Brasil. e-mail: amtsouza@pharma.ufrj.br & [barbaraabrahim@pharma.ufrj.br](mailto:barbaraabrahim@pharma.ufrj.br)

**Data availability statement**

Data sharing is not applicable for this publication; no new clinical data were generated in this modeling study.

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3862 words, 6 tables, 7 figures

**What is already known about this subject**

* Liraglutide is the glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for type 2 diabetes pediatric therapy, although with difficult treatment adhesion.
* Semaglutide is approved for adults with type 2 diabetes, with superior treatment adhesion and efficacy compared to liraglutide.
* Semaglutide pharmacokinetic (PK) data for the pediatric population is still lacking.

**What this study adds**

* A physiologically-based pharmacokinetic (PBPK) model of subcutaneous semaglutide was developed for predicting its PKs in children and adolescents.
* The pediatric PBPK simulations indicated that 10-14 years old children, with healthy body weights, presented semaglutide peak concentrations outside the target range observed in adults at the reference dose.

**Abstract**

**Aim**: Develop PBPK models of semaglutide to estimate the pharmacokinetic profile for subcutaneous (SC) injections in children and adolescents with healthy and obese body weights.

**Methods**: Pharmacokinetic modeling and simulations of semaglutide SC injections were performed using the Transdermal Compartmental Absorption & Transit (TCAT™) model implemented in GastroPlus™ v.9.5 modules. A PBPK model of semaglutide was developed and verified in the adult population, by comparing the simulated plasma exposure with the observed data, and further scaled to the pediatric populations with normal and obese body weight.

**Results**: The Semaglutide PBPK model was successfully developed in adults and scaled to the pediatric population. Our P-PBPK simulations indicated a significant increase in Cmax values for the 10-14 years pediatric population with healthy body weights, which was higher than the observed values in adults at the reference dose. Since gastrointestinal adverse events are related to increased semaglutide exposure, peak concentrations outside the target range may represent a safety risk for this pediatric age group. Besides, PBPK models indicated that body weight was inversely related to semaglutide exposure in children and adolescents, which is in line with the results observed in population pharmacokinetic studies in adults.

**Conclusion**: Due to the absence of semaglutide pharmacokinetic data for the pediatric population, these PBPK models will aid in the development of dosing regimens and sampling times. Thus, increasing the efficiency of future pediatric clinical trial studies which can be replaced or improved by PBPK models.

**1. Introduction**

Diabetes mellitus (DM) is the third most common disease in children and adolescents under 18 years old [1] due to the increase in obesity and lack of physical activity in this population (DM2) [2,3]. Currently approved therapy only includes the use of metformin and more recently, liraglutide [4-7], in which there is still concern related to treatment adhesion.

Recently, Semaglutide (Ozempic®) was approved with superior long-term glycemic and body weight control capacity compared to liraglutide [8-11]. Nevertheless, liraglutide is the glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for pediatric therapy [12]. The recruitment of young people with DM2 for clinical trials is relatively recent and has presented limited success [13,14]. Indeed, a major challenge for academics and the pharmaceutical industry is to achieve a safe and effective dose in pediatric patients [15].

Physiologically Based Pharmacokinetic (PBPK) models are a valuable approach for integrating known physiological changes that alter drug disposition in children with drug-specific parameters in an untested scenario. [16-18]. Consequently, pediatric PBPK (P-PBPK) models are advantageous to support dosing decisions during pediatric clinical trials [19-21] and are applied in a variety of pediatric patient groups [19-23].

To fulfill the gaps in our knowledge of the use of semaglutide in the pediatric population, and considering the difficulties in carrying out these studies, we developed P-PBPK models of semaglutide to improve the ability surrounding pediatric drug treatment.

**2. Methods**

In this study, a PBPK model of semaglutide was developed and verified in the adult population, by comparing the simulated plasma exposure with the observed data, and further scaled to the pediatric population. The final P-PBPK model was developed to enable the estimation of semaglutide doses. The workflow of the model development is presented in Figure 1.

***Software***

Pharmacokinetic modeling and simulations of SC injections of semaglutide were performed using the Transdermal Compartmental Absorption & Transit (TCAT™) model implemented GastroPlus™ v.9.5 modules (Simulations Plus, Inc., Lancaster, CA).

***Input data***

Drug-specific physicochemical properties were obtained from the literature and *in silico* predictions (Table 1) [24, 25]. The model development strategy employed a "middle-out" approach, where model parameterization was guided by clinical observations in humans. The plasma concentrations of semaglutide were extracted from the original figure reported previously by Jensen *et al* (2017) [25]using Web Plot Digitizer 4.2 [26] and used in the PKPlus™ module in GastroPlus™ to build a pharmacokinetic (PK) model.

Physiologies, including age- and body-weight-matched organ weights, volumes, and blood perfusion rates, were generated by the PEARTM Physiology,implemented in GastroPlus™ (Tables 1 and 2). PBPK models development and workflow followed FDA guidance [27-29].

***PBPK model development and verification for intravenous and SC injections of semaglutide in healthy adults (Sema-1).***

A detailed online literature search was executed to shortlist the published literature in which concentration-time profiles and pharmacokinetic data of semaglutide were available after intravenous (IV) and SC administration. First, drug disposition was modulated after IV administration, and the adult PBPK model performance was subsequently evaluated based on the concentration versus time data extracted from the literature [30] to promote confidence in the model parametrization. As semaglutide is a relatively large (4.1 kDa) and hydrophilic (logP: -17) peptide, the permeability-limited tissue model was considered for all tissues, where the kinetics of drug uptake into the tissue is modeled as time-dependent. Physical-chemical properties of semaglutide and physiological data matching the age and body weight average of the subjects in the clinical study were also used as input. No adjustments were performed on organ/tissue sizes and blood flow for clearance (CL) and steady-state volume of distribution (Vss) prediction (Tables 1 and 2). Then, the PBPK model was also validated for the subcutaneous administration route based on the concentration versus time data extracted from the literature [25] and reported pharmacokinetic parameters from different clinical studies [24, 25, 31]**.**

***Model Performance Evaluation.***

The Sema-1 model's performance was verified by calculating the fold-error (FE) [34], an observed/predicted ratio (ratioObs/Pred) of calculated PK parameters (Cmax, Tmax, and AUC) compared to the reported pharmacokinetic parameters after intravenous [30] and subcutaneous administrations [24, 25, 31]. Prediction accuracy of pharmacokinetic parameters was assessed using a two-fold error range from the observed values for model predictions, a criteria generally applied in PK predictions [34].

***Parameter Sensitivity Analysis.***

If the PBPK model data were not close enough to the observed data, a parameter sensitivity analysis (PSA) was performed to understand the effect of selected PK parameters within the Sema-1 model. The PSA was conducted with subcutaneous tissue compartment physiological parameters, such as subcutaneous effective depot Volume (mL), adipose tissue subcutaneous blood flow (sATBF), subcutaneous permeability-surface area, and partition coefficient of adipose tissue. Thus, an investigation with a virtual population matching the mean demographic parameters of the clinical study by Jensen *et al.* was performed. The extent of subcutaneous tissue compartment physiological parameters and the influence on Tmax values, considering the selected parameter range, was evaluated.

***Pediatric scaling PBPK models (Sema-2 and 3).***

For the development of the pediatric PBPK (P-PBPK) models, the validated adult PBPK model was scaled down to the pediatric populations of ages 10–17 years, with normal (Sema-2) and obese (Sema-3) body weights. Taking into account age-dependent physiological differences, pediatric populations were built-in into GastroPlus 9.5 internal module called PEAR Physiology™ and grouped as children (10-12 years old), early adolescents (13-14 years old), and adolescents (15-17 years old) subpopulations. Each virtual age group consisted of 50 females and males. The PK parameters used as input to the adult Sema-1 model were kept constant for the P-PBPK models. During the generation of the virtual pediatric population and simulation of P-PBPK model, physiological information related to this age group (10-17 years), including weight, volume, density, and perfusion for each tissue, were scaled by PEARTM itself according to the pediatric age. The demographic characteristics of the virtual pediatric population, which were based on the CDC growth charts and tables for children, are given in Table 2 [35].

For the virtual population of obese children (Sema-3), two data sources were used to build a simulation dataset. As the prevalence of obesity has increased significantly since the 1980s, when data for the 2000 CDC growth charts were collected, a greater number of children are above the CDC-defined obesity cut-off. Accordingly, pediatric body weights were also adjusted based on more recent data reported in the National Center for Health Statistics (NHANES) (Table 2) [36]. The increase of kidney volume and liver volume in obese children, implemented in the gastroplus virtual population, was in accordance with the reported percent increase in the literature [37-39]. Because of a lack of composition data in children with obesity (e.g., percent lipids, protein, and water within an organ), organ composition was modeled the same way as in existing virtual children without obesity in Gastroplus. Cardiac output (an aggregate measure of blood flow to all perfused organs) is often higher in obesity, due to an augmented stroke volume and an increase in heart rate [40-45]. The simulated cardiac output for the obese pediatric virtual population was similar to the reported values in the literature for obese children (4.4–7.3 L/min) (Table 3) [40-45]. Obesity alone can influence glomerular filtration rate (GFR). However, while a population study in Turkey found that obese children and adolescents (5 to 18 years old) presented lower eGFR values compared to those with normal BMI [46], Bonito et al. and Sawamura et al did not find any significant association between eGFR and BMI in children and adolescents [47,48]. Thus, due to conflicting results from publications regarding BMI influence on pediatric GFR, the same values were considered for the normal and obese pediatric virtual populations. Still, the Sema-2 and Sema-3 simulated values for pediatric GFR were consistent with data reported in the literature for [47,48] (Table 3). No additional changes in hematocrit with obesity were included in the pediatric virtual population, as literature data showed no significant change in pediatric hematocrit across a wide BMI range [37, 49] (Table 3). According to literature data, albumin concentrations between children with and without obesity showed no observable difference across a wide BMI range [37, 49]. Thus, no additional changes in albumin concentrations with obesity were incorporated into the virtual population.

**3**. **Results**

**3.1. Development and performance evaluation of PBPK Sema-1 model: Single dose of intravenous semaglutide in adults.**

To bypass the complexity of absorption, the IV approach was adopted first which yielded distribution and elimination patterns comparable to observed data. Model performance evaluation was carried out using superimposition model-based predictions with observed data [30] (Figure 2). The PBPK model successfully predicted the PK of intravenous semaglutide in adults. The mean predicted AUC0-t (ratioObs/Pred) and Cmax values (ratioObs/Pred) were within 1.4-fold of the clinically-reported value (Table 4) [30].

**3.2. Development and performance evaluation of PBPK Sema-1 model: Single dose of subcutaneous semaglutide in adults.**

After successful intravenous data assessment, the clinical PK profile of the subcutaneous route of administration for semaglutide, after a single simulation, was evaluated. The model showed a discrepancy of Tmax (Figure 4A). Then, a PSA was carried out to explore which intrinsic physiological factors might be affecting the drug disposition. The semaglutide SC injection model showed sensitivity regarding sATBF and Kp where an increase in Kp values and a decrease in sATBF resulted in prolonged Tmax values. Additionally, the other subcutaneous tissue compartment physiological parameters investigated, such as effective depot volume (mL) and subcutaneous permeability-surface area, demonstrated minor to no sensitivity on Tmax. Thus, these parameters were kept as default. The sATBF is strongly related to tissue metabolic functioning and presents a great inter-individual variability, with reference values ranging ​​between 0.56-10.41 mL/min/100g of tissue for healthy adults [50, 51].

The Kp values ​​were calculated based on the Poulin equation for drug partitioning in the extracellular space [52]. In the absence of experimental data for semaglutide and considering that this drug distributes in plasma and peripheral tissues to the same extent as albumin [30], the average extravascular/intravascular ratio of albumin of 1.43, with experimental values ​​ranging from 1.17 to 1.76 [53] was used.

A 3D PSA was carried out to analyze the combined effect of sATBF and Kp on Tmax values, allowing the most appropriate adjustment for each parameter (**Figure 3**). As a result, the sATBF and the partition coefficient, both of adipose tissue, underwent adjustments for correlation with experimental data, demonstrating the relevance of these parameters in the semaglutide PBPK model development. Regarding the Kp, the adjustment from the GastroPlus calculated value of 0.06 to 1.76 resulted in the simulation of the pharmacokinetic profile closest to the experimental one [25] (**Figure 4**). The distribution of the drug between the extracellular and intracellular space of this administration compartment follows the model of slow passive diffusion in the permeability-limited tissue model [54]. The partition coefficients of the other tissues were kept. Regarding sATBF, the adjustment from 3.77 mL/min/100g, supplied as default, to the value of 0.6 mL/min/100g, along with the adipose tissue Kp adjustment, allowed the best correlation with the experimental results (**Figure 4B**).

Sema-1 model performance evaluation was carried out using superimposition model-based predictions with observed data from three clinical studies [24, 25, 31], considering virtual populations matching physiological data from the clinical studies (**Table 5; Figure 5**). The PBPK model successfully predicted the PK of semaglutide in adults. The mean predicted AUC0-t (ratioObs/Pred 0.95-1.19) and Cmax values (ratioObs/Pred 0.92-0.99) were within 1.25-fold of the clinically-reported values in the three reference studies (Figure 5, Table 3). Although the adjusted model led to higher AFE for Tmax considering two clinical studies, Jensen *et al*, 2017 (ratioObs/Pred = 1.84) and NN9535-4010 (ratioObs/Pred = 3), the values were within the range observed in the clinical studies. Indeed, this was the parameter with the greatest inter-individual variability in semaglutide clinical studies (**Table 5**) [8, 24].

**3.2 PBPK models for children and adolescents: Sema-2 and Sema-3**

According to simulation results, Tmax and AUC0-840h presented little variation over the pediatric population (10-17 years old), with normal and obese body weights, with mean values ​​between 25 and 35 h, and 9.96 and 11.97 µg-h/mL, respectively, which were within the range stated in clinical studies with adults [24, 25, 31]. Differently, Cmax presented the greatest variation with age, ranging from 0.085 to 0.029 µg/mL (**Table 6**). Within this population, the 10-14 years with normal body weight (Sema-2) presented the highest Cmax values, which were higher than the range stated in clinical studies with adults at the reference dose of 0.5 mg (**Table 6**, **Figures 6** and **7**).

The obese pediatric population (Sema-3) presented an average increase of 6.4 hours in Tmax values in relation to children with normal body weight (Sema-2) at the same age range (Table 6), which remained in the range stated in clinical studies with adults. Regarding the absorption extent (AUC), little variation was observed with the increased body weight (Table 6). Cmax showed the greatest variation with body weight, with a mean increase of 0.033 µg/mL for obese children compared to children with normal body weight in the same age range (Table 6). Notably, the plasma concentrations of semaglutide decreased in obese children and adolescents in all the studied age ranges, with values achieving the range stated in adult clinical studies, even for the 10-12 and 13-14 years old ranges (**Figures 6** and **7**).

**4. Discussion**

Given the limited opportunities to collect data in children, modeling and simulation methodologies are being utilized by academia, industry, and regulatory agencies as powerful tools to optimize resources to design meaningful pediatric clinical studies for drug development [55-58].

Dose selection is the most common pediatric drug development application followed by formulation. The use of P-PBPK models for initial dose extrapolation prior to undertaking clinical trials in children has been steadily increasing in the last few years and is viewed as a low/medium impact application of this approach in the recent European Medicines Agency guidelines [59, 60]. P-PBPK models have been used for dose projection in different age groups based on adult exposure in clinical and drug development settings [58, 59, 61, 62].

In the present study, the P-PBPK model was developed using best practice with model verification and modification following a predict–learn–confirm paradigm, refining the model based on adult data before undertaking simulations in pediatrics [59, 63]. This is the first time a PBPK model has been developed for semaglutide, a drug that represents a T2D therapy, safe and efficacious. Although the STEP-4 Teen trial closed in March 2022 ([https://clinicaltrials.gov/ct2/show/NCT04102189](https://clinicaltrials.gov/ct2/show/%20NCT04102189)), no pharmacokinetic and dose adjustment data have been released up to now.

The adult PBPK model was successfully developed for semaglutide, based on the good prediction of the concentration-time profiles after a single intravenous (IV) and subcutaneous administration of semaglutide. First, the pharmacokinetics simulation with IV application was carried out, as it provides disposition kinetics without the interference of complexities arising from absorption. In the next step, a PBPK model for semaglutide was developed based on PK characteristics in healthy adults (Sema-1) and evaluated using PK data from three different clinical studies for the subcutaneous administration route [24, 25, 31].

To the development of the Sema-1 model, it was needed to perform a PSA that pointed out the sATBF and the partition coefficient, both of adipose tissue, as critical parameters for the model development. These parameters are directly related to the SC administration, where the drug is deposited within the interstitial fluid of the extracellular matrix and needs to diffuse to the nearest blood or lymphatic capillary. Literature supports redefining parameters in order to accomplish a similar-to-desired pharmacokinetic profile [64, 65]. Thus, sATBF and the adipose tissue partition coefficient were adjusted from a range of literature values [50, 51, 53], assuming that this drug distributes in plasma and peripheral tissues to the same extent as albumin [30]. As a result, sATBF of 0.6 mL/min/100g and adipose tissue Kp of 1.76 minimized variation between the fitted and reference pharmacokinetic profiles [25]. Afterward, with the ratioObs/Pred of Tmax, AUC, and Cmax within the two-fold range performance [34, 66], the established Sema-1 model adequately described the observed PK of semaglutide after a single SC dose in healthy adults. It is important to highlight that, although the adjusted model led to high AFE values for Tmax (0.79-3), the simulated values were within the observed range of clinical studies. Indeed, according to submitted clinical studies for the American and European regulatory authorities (FDA and EMA), after SC injection of a single 0.5 mg dose of semaglutide in healthy men, the drug was slowly absorbed into the systemic circulation and maximum concentrations were reached between 24 and 122 hours [8, 24]. Thus, this variability was expected due to the high inter-individual variability observed by clinical studies [8, 24].

In P-PBPK Sema-2 of 10-14 years old, the Cmax values were above the reference range observed for adults at 0.5 mg (**Figures 6** and **7**). This age group corresponds to the developing children subpopulation [67], which presents a smaller thickness of SC tissue and a higher perfusion rate. These features surely play a role in the higher exposure of semaglutide in this subpopulation compared to older children and adults [68] being of particular concern due to the higher probability of gastrointestinal adverse events (GIAEs) associated with this drug. In adults, GIAEs are dose-dependent most notably with nausea and vomiting. Another consistent finding associated with semaglutide treatment is a subtle and asymptomatic increase in plasma lipase and amylase level, which occurs within hours of administration [69, 70]. In a 26-week randomized controlled trial, subcutaneous semaglutide dose-dependently increased lipase levels by 9 to 36% [71]. Although an increase in enzyme levels was not associated with the occurrence of pancreatic events in trials with liraglutide, such studies have not yet been conducted for semaglutide [70]. Thus, peak concentrations outside the target range may represent a crucial risk for the developing children subpopulation.

Epidemiologic studies have reported a strong relationship between obesity and DM2 in youth [72-75]. P-PBPK approach is remarkably helpful for examining the suitability of adjusting the treatment dose for pediatric-specific population subsets, particularly those expected to have exposures at the low and high extremes, such as high vs low body weight, which has been shown to be of importance for semaglutide exposure [76]. So, we also analyzed the influence of body weight on semaglutide exposure through a pediatric virtual population simulation of obese children and adolescents. A comparison between the obese and normal body weight pediatric virtual populations indicated that body weight is the covariate of importance for semaglutide pharmacokinetics, especially for younger children. In all the age groups studied, body weight was inversely related to semaglutide exposure, corroborating the consensus on the influence of increased body weight on decreased semaglutide exposure in adults [8, 9, 24]. Body weight was also the main covariate affecting liraglutide exposure in both adolescents and adults, which is the drug from the GLP-1 analogs class recently approved for the treatment of pediatric patients 10 years or older [77, 78]. Covariate analysis showed that subjects with low body weight will achieve higher liraglutide exposure than subjects with high body weight, suggesting that differences in clinical response to liraglutide may be associated with differences in exposure [77, 78].

The 10-14 years old (Sema-2) presented the highest Cmax values, while the 15-17 years old adolescents with obese body weights presented the lowest values for this PK parameter (0.022-0.037 µg/mL) (**Table 6**, **Figures 6** and **7**). Despite that, the mean Cmax value (0.029 µg/mL) simulated for this older age group was within the reference range (0.028–0.056 µg/mL) in adults, but lower than the median Cmax value (0.0447 µg/mL) observed in adults (**Table 6**). Although body weight was found to be the most important covariate affecting exposure, no dose adjustments were necessary for obese adults that fell within the lower exposure values of the observed reference range [76]. Even if the predicted Cmax for these obese 15-17 years-old adolescents indicated a lower exposure compared to normal body weights children and adults, dose adjustment should not be required for this age group, since the Cmax values were within the reference range observed in adults.

All P-PBPK Sema-2 models, from 10 to 17 years old, presented a high variation of Cmax with age (**Table 6**), which indicates an increase in drug exposure inversely correlated to age. However, this variation might be related to body weight increases through 10 to 17 years instead of age. Consequently, dose adjustment based on age alone is not recommended.

The plasma concentrations of semaglutide decreased in obese children of all ages studied (Sema-3 models) compared to children with normal body weights (Sema-2) (**Table 6**), which may be correlated with the thickness of the adipose tissue of this population. In adults, body weight loss increased linearly with increasing semaglutide exposure, with a relative weight loss from baseline of ~6.5% for the highest exposure quantile and a predicted weight loss of ~8% for participants with exposure at the upper end of the exposure range [76]. Since semaglutide reduces body weight, the predicted higher exposure for normal body weights children, especially for the 10-14 years old group, is expected to increase even more throughout the treatment compared to baseline values. This result is of particular concern due to the higher probability of gastrointestinal adverse events (GIAEs), which were exposure-dependent in adults, such as the exposure-response analysis of vomiting, which showed an increased proportion of participants with events and number of events with increasing exposure [76].

Tmax values were reduced in the Sema-3 group by an average of 3.2 hours in relation to the healthy body weight pediatric population but still remained in the range stated in clinical studies (**Table 6**, **Figure 6**). It is feasible that the amount of subcutaneous fat influences the absorption rate due to less vascularization of adipose tissue. The increased skinfold thickness as well as higher BMI has also been associated with delayed absorption of subcutaneous administered drugs [51, 79, 80, 81].

Our simulation results indicated that different dosage regimens must be considered for the younger children in future pediatric clinical studies, in order to avoid the GIAEs associated with high semaglutide exposure. Moreover, the heterogeneity in weight loss response related to semaglutide use must be given due consideration, as the semaglutide exposure increased significantly in the younger children with lower body weight.

**5. Conclusion**

Considering the absence of pharmacokinetic studies of semaglutide for pediatric patients with DM, herein we reported P-PBPK models with healthy and obese children to contribute to a clinical trial of first-in-child dosing. P-PBPK simulations indicated that 10-14 years old children, with healthy body weights, presented semaglutide peak concentrations outside the target range observed in adults at the reference dose of 0.5 mg. This result is of particular concern due to the higher probability of gastrointestinal adverse events, which were exposure-dependent in adults. These simulations also highlighted that body weight was inversely related to semaglutide exposure in children and adolescents, corroborating the results observed in clinical studies with adults. Since increased semaglutide exposure is related to gastrointestinal adverse events, our results might be helpful in the design of future pediatric clinical studies, in which adequate dosage regimens of semaglutide should be considered, particularly for younger children. Indeed, this study corroborates the improvement of the pediatric PBPK models, allowing academia, industry, and regulatory agencies to apply pediatric efficacious and safe doses in diabetes treatment.

***Conflict of Interest Statement***

The authors declare that they have no competing interests.

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***Author Contributions***

A.M.T.S and B.A.A.V. conceived the initial idea and designed the research. T.R.M. performed and analyzed the PBPK studies. T.H., D.S.C.P. and T.F.S.D contributed with the statistical and *in silico* analysis. C.R.R. and L.M.C. supported all the computational work. A.M.T.S. and B.A.A.V. finalized the manuscript and all authors approved it.

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**Table 1.** Input parameters used to build the PBPK model for semaglutide intravenous and subcutaneous injection in adults (Sema-1 model).

|  |  |  |
| --- | --- | --- |
| Parameter | Value | Source |
| Dosage Form | Intravenous (bolus)/ subcutaneous (SQ): solution | - |
| Dose volume (mL) | 0.37 (SQ) | [8] |
| Single Dose (mg) | 0.25 (IV)  0.5 (SQ) | [25, 30] |
| Log P | -17 | [32] |
| pKa | 2.74 (acid) and  12.26 (base) | [33]  [Drug Bank (DB13928)](https://www.drugbank.ca/drugs/DB13928) |
| Chemical formula | C187H291N45O59 | [33]  [Drug Bank (DB13928)](https://www.drugbank.ca/drugs/DB13928) |
| Molecular weight (g/mol) | 4113.64 | [33]  [Drug Bank (DB13928)](https://www.drugbank.ca/drugs/DB13928) |
| Solubility(mg/mL) | 1.34 at pH: 7.4 | [8] |
| Human blood-to-plasma ratio (B/P) | 0.55 | [32] |
| Unbound percent in human plasma (%) | 0.36 | [32] |
| Clearance (CL/F) (L/h) | 0.041 | pKplus |
| Steady-state volume of distribution (Vss) (L) | 8.6 | pKplus |
| Half-life (t½) (h) | 153 | pKplus |
| Subcutaneous tissue / water partition coefficient | 176 | GastroPlus (Calculated) |
| Adipose tissue thickness (microns) | 3538.7 | Default (GastroPlus) |
| Dosing region | Abdomen | - |
| Subcutaneous adipose tissue blood flow (sATBF) (mL/min/100g subQ) | 0.6 | Fitted |
| Partition coefficient of the adipose tissue (Kp) | 1.76 | Fitted |

**Table 2**. Characteristics of the population used for Semaglutide PBPK model development.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Population | Population Size (n) | Proportion of female (%) | Age  (years) | BMI  (kg/m²) | Body Weight (Kg) | Dose  (mg) | Application | References |
| European | 7 | 0 | 48-64 | 21.7-29.7 | 62.6 - 107.3 | 0.5 | Single s.c dose | [25] |
| American | 14 | 40 | 45-63 | 25.1-33.3 | 65.8 - 104 | 0.5 | Single s.c dose | [31] |
| European | 28 | 50 | 18-55 | 18.5-30 | - | 0.5 | Single s.c dose | NN9535-4010 [24] |
| Children | 100 | 50 | 10-12 | 15-20 | 24-42 | 0.5 | Single s.c dose | - |
| Children | 100 | 50 | 10-12 | 23-26 | 55-65 | 0.5 | Single s.c dose | - |
| Early adolescents | 100 | 50 | 13-14 | 15-23 | 48-60 | 0.5 | Single s.c dose | - |
| Early adolescents | 100 | 50 | 13-14 | 26-28 | 70-76 | 0.5 | Single s.c dose | - |
| Adolescents | 100 | 50 | 15-17 | 18-24 | 53-70 | 0.5 | Single s.c dose | - |
| Adolescents | 100 | 50 | 15-17 | 26-30 | 80-105 | 0.5 | Single s.c dose | - |

**Table 3.** Mean simulated values for liver and kidney organ volumes, hematocrit, cardiac output (CO), and glomerular filtration rate (GFR) for the virtual populations of adults and pediatrics with healthy and obese body weight.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Population  (Years-old) | Body Weight | Hematocrit (L/L) | Liver Volume (L) | Kidney Volume (L) | CO (L/min) |
| 56 | Healthy | 0.45 | 1405.2 | 236.56 | 5.4 |
| 10 | Healthy | 0.43 | 634.41 | 113.38 | 2.6 |
| 10 | Obese | 0.43 | 932.96 | 166.73 | 4.4 |
| 11 | Healthy | 0.44 | 845.454 | 114.124 | 3.5 |
| 11 | Obese | 0.44 | 1014.28 | 179.338 | 4.7 |
| 12 | Healthy | 0.44 | 704.794 | 123.75 | 3.7 |
| 12 | Obese | 0.44 | 1112.83 | 195.394 | 4.9 |
| 13 | Healthy | 0.44 | 861.485 | 148.69 | 4.5 |
| 13 | Obese | 0.44 | 1263.51 | 218.078 | 5.4 |
| 14 | Healthy | 0.45 | 938.063 | 165.983 | 4.8 |
| 14 | Obese | 0.45 | 1355.98 | 239.931 | 5.5 |
| 15 | Healthy | 0.45 | 995.495 | 181.594 | 5.4 |
| 15 | Obese | 0.45 | 1423.75 | 259.714 | 6.9 |
| 16 | Healthy | 0.45 | 1072.07 | 201.726 | 5.4 |
| 16 | Obese | 0.45 | 1479.08 | 278.309 | 7.0 |
| 17 | Healthy | 0.45 | 1148.65 | 222.171 | 5.5 |
| 17 | Obese | 0.45 | 1523.66 | 294.71 | 7.3 |

**Table 4.** PBPK Sema-1 performance evaluation comparing predicted and observed pharmacokinetic parameters for semaglutide after intravenous (bolus) dose of 0.25 mg in healthy adults.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Single IV dose  (mg) | Cmax (µg/mL) | | | AUC0-t (µg-h/mL) | | | AUC0-inf (µg-h/mL) | | | References |
| Observed | Predicted | Mean  Ratio  Obs/  Pred | Observed | Predicted | Mean  Ratio  Obs/Pred | Observed | Predicted | Mean  Ratio  Obs/Pred |
| 0.25 | 0.082 | 0.102 | 0.80 | 8.77 | 6.4 | 1.37 | 7.5 | 6.2 | 1.21 | [30] |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Single s.c dose  (mg) | Cmax (µg/mL) | | | | | | Tmax (h) | | | | | | AUC0-t (µg-h/mL) | | | | | | References |
| Observed | | Predicted | | | Mean  Ratio  Obs/  Pred | Observed | | Predicted | | | Mean  Ratio  Obs/  Pred | Observed | | Predicted | | | Mean  Ratio  Obs/Pred |
| Mean (CV %) | Min-Max | Mean (CV %) | Min-Max | 90 % Cl | Mean (CV %) | Min-Max | Mean (CV %) | Min-Max | 90 % Cl | Mean (CV %) | Min-Max | Mean (CV %) | Min-Max | 90 % Cl |
| 0.5 | 0.045 (18.2) | 0.034-0.051 | 0.045 (14) | 0.036-0.056 | 0.041-0.050 | 0.99 | 56 | - | 30.4 (14) | 24-37 | 27.2-33.7 | 1.84 | 12.58 (12) | 11.1-14.1 | 11.35 (18) | 7.9-15.5 | 9.75-13.6 | 1.11 | [25] |
| 0.5 | 0.042 (35) | 0.028-0.057 | 0.044 (15) | 0.032-0.058 | 0.040-0.047 | 0.95 | 24 (8.6) | 20.6-27.38 | 30.42 (14) | 24-38.5 | 28.1-32.3 | 0.79 | 10.7 (27) | 7.8-13.59 | 11.28 (25) | 6.4-16.3 | 9.65-13.0 | 0.95 | [31] |
| 0.5 | 0.047  (18.9) | 0.038-0.056 | 0.051 (14) | 0.040-0.067 | 0.050-0.54 | 0.92 | 95.62 | 24-121 | 30 (11) | 24,7-38.8 | 28.4-30.6 | 3 | 14.08 (24) | 10.7-17.45 | 11.8 (29) | 6.10-19.5 | 10.70-12.90 | 1.19 | [24] (NN9535-4010) |

**Table 5.** PBPK Sema-1 performance evaluation comparing predicted and observed pharmacokinetic parameters for semaglutide after subcutaneous injection in healthy adults.

**Table 6.** Predicted pharmacokinetic parameters for semaglutide, after SC injection, in children aged 10 to 17 years with normal and obese body weights.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Pediatric Virtual Population | | Pharmacokinetic Parameters | | | | | | | | |
| Age | Body Weight | Cmax  (µg/mL) | | | Tmax (h) | | | AUC 0-t (µg-h/mL) | | |
| Mean  (CV %) | Min-  Max | 90 % Cl | Mean  (CV %) | Min-  Max | 90 % Cl | Mean  (CV %) | Min-  Max | 90 % Cl |
| 10-12 | Healthy | 0.076 (18) | 0.050-0.12 | 0.073-0.077 | 25 (14) | 19-38 | 24.5-25.6 | 11.55 (32) | 4.90-23.0 | 11.09-12.20 |
| 10-12 | Obese | 0.041  (11) | 0.031-0.053 | 0.041-0.042 | 31.3 (13) | 24-43 | 30.6-32 | 11.6 (29) | 6.7-18.9 | 10.06-11.14 |
| 13-14 | Healthy | 0.085 (10) | 0.063-0.11 | 0.084-0.086 | 25 (13) | 17.4-33.4 | 25-26 | 11.97 (29) | 5.26-21.22 | 11.4-12.5 |
| 13-14 | Obese | 0.036 (12) | 0.028-0.048 | 0.036-0.037 | 33 (11.6) | 25-42 | 32-33 | 10.74 (22.4) | 6.0-20.4 | 10.3-11.1 |
| 15-17 | Healthy | 0.043 (12) | 0.032-0.058 | 0.042-0.044 | 30 (13) | 23.3-43.8 | 30-31 | 10.54 (28) | 5.7-20.0 | 10.0-11.0 |
| 15-17 | Obese | 0.029 (12) | 0.022-0.037 | 0.029-0.030 | 35 (13) | 25.6-45 | 34-35 | 9.96 (21) | 5.25-16.02 | 9.38-10.10 |

**Figure 1.** Adult and pediatric modeling workflow. IV: intravenous, SC: subcutaneous, sATBF: SC adipose tissue blood flow, Kp: partition coefficient of adipose tissue.

**Figure 2.** Comparison of predicted (continuous line) and observed (circles) plasma concentration-time profiles of a single intravenous (bolus) dose of 0.25 mg semaglutide, in healthy adult men.

**Figure 3**. Tridimensional Parameter Sensitivity Analysis (PSA) of the effect of subcutaneous adipose tissue blood flow (sATBF) and partition coefficient of adipose tissue (Kp) on Tmax values.

**Figure 4**. Comparison of predicted (continuous line) and observed (circles) plasma concentration-time profiles of a single dose SC injection of 0.5 mg semaglutide, in healthy adult men. (**A**) Simulation using default values for SC adipose tissue blood flow (sATBF) and partition coefficient of adipose tissue, i.e., 3.77 mL/min/100g and 0.06, respectively and (**B**) Adjusted conditions, i.e., 0.6 mL/min/100g and 1.76, respectively.

**Figure 5.** Model performance verification with clinical studies: (**A**) Jensen *et al*, 2017, (**B**) Marbury *et al*, 2017 and (**C**) NN9535-4010. Simulated (*black line*) and observed data (*points*) mean plasma concentration–time profile after a single 0.5 mg SC dose of semaglutide. The predicted plasma concentration time profile is shown as a solid line. The shaded green regions are the 90% model prediction interval.

**Figure 6.** Mean pharmacokinetic parameters and CVs% predicted after a single SC 0.5 mg dose for the virtual pediatric population of 10-12 years old in blue, 13-14 in purple, and 15-17 years old in green. Reference adult values range at 0.5 mg single SC dose, such as 0.028–0.056 µg/mL for Cmax, 7.8–17.45 µg.h/mL for AUC0–inf, and 24-122h for Tmax, are represented as dotted lines.

**Figure 7.** Mean simulated plasma concentrations profiles of semaglutide (black line), following an SC injection of a single 0.5 mg dose for (**A**) 10-12, (**B**) 13-14, and (**C**) 15-17 years old pediatric population with normal average body weights (left) and obese body weights (right), and observed experimental data in healthy adults (pink dots). The shaded green regions are the 90% model prediction interval.