# Chapter 6

# Evaluation and optimisation of a semi-physiological pharmacokinetic model for prediction of the pharmacokinetics in special populations, including children aged between 6 and 18 years

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*To be submitted*

## Abstract

Previously, a semi-physiological framework has been proposed to predict the pharmacokinetics of solifenacin in hepatic and renal impaired patients by considering disease-related changes in physiology. In this investigation, the application of the semi-physiological approach is evaluated using tamsulosin for the prediction of the pharmacokinetics affected not only by disease-related (i.e., hepatic and renal impairment) but also by growth-related (i.e., children from 6 to 12 years) changes in physiology. The semi-physiological framework was applied using data on the plasma and urine concentrations and the plasma free fraction in healthy adult subjects. The analysis was performed using non-linear mixed effect modelling and relied on the utilization of a general partitioning framework to account for binding to plasma-proteins together with principles from physiology that apply to absorption, distribution, metabolism and excretion. The prediction of the pharmacokinetics in the investigated special populations only required adjustment of the physiological parameters that are known to change upon disease or growth. Visual predictive checks showed that the proposed framework was able to adequately predict the pharmacokinetics of tamsulosin in hepatic and renal impaired patients and in children. Predictions in children were placed into perspective by comparing it with the allometric scaling approach. Predictions were in general similar but a slight improvement was observed in the prediction of half-life and the inter-individual variability when using the semi-physiological approach. In conclusion, this investigation showed that the semi-physiological framework is adequate for prediction of altered pharmacokinetics resulting from disease and growth

## Introduction

Multiple alterations in the physiology resulting from disease or growth may influence the pharmacokinetics of a drug. For example, hepatic diseases are known to cause alterations in the intrinsic capacity of the liver to metabolize drugs, in the perfusion of the liver, in the plasma protein binding and in the renal function [1]. Knowledge on these disease-related changes has constituted the basis for the development of system models (e.g. (semi-)physiologically based pharmacokinetic models) for the prediction of the influence on the pharmacokinetics of drugs [2-4]. Further, knowledge on growth-related changes have also been incorporated in such models to predict the variation in the pharmacokinetics of drugs in children [5-7]. When solely growth-related changes impact the pharmacokinetics, reduction of the physiological system to an allometric relationship with body weight as covariate is commonly applied [8]. This approach, however, is of limited utility to predict the changes in pharmacokinetics resulting from different types of changes in the physiological system [9, 10].

Recently, a semi-physiological framework to assemble system and drug characteristics has been proposed [4]. This semi-physiological framework combines a descriptive compartmental model structure with a partitioning framework to describe the influence of protein binding in plasma. In addition, key principles of the physiology that apply to absorption, distribution, metabolism and excretion are incorporated into the model. Incorporation of these physiological features allows predicting the influence of disease and growth related factors by adjusting the values of physiological parameters. In addition, considering only key principles of the physiology, allows the use of non-linear mixed effect modeling which enables estimation of population and random-effect parameters in order to estimate unknown sources of variability. Considering only key principles of the physiology was shown not to hamper the applicability of the approach to predict the pharmacokinetics of solifenacin in hepatic and renal impaired patients [4]. Another potential application of this approach yet to be investigated is the prediction of the pharmacokinetics upon growth-related changes in the physiology.

In the current investigation, the applicability of the semi-physiological framework to predict changes in the pharmacokinetics in hepatic and renal impaired patients and in pediatric patients with dysfunctional voiding from 6 to 12 years was evaluated. To our knowledge, dysfunctional voiding is not expected to influence the pharmacokinetics of tamsulosin. The predictions in children were placed into perspective by comparing the semi-physiological framework to the allometric scaling approach. In both cases, tamsulosin was used as a model drug. Tamsulosin hydrochloride (Flomax®; Omnic®) is an $\alpha_{1a}$-selective alpha blocker used in the symptomatic treatment of benign prostatic hyperplasia (BPH) in adults and investigated for symptoms of dysfunctional voiding in children. Tamsulosin is extensively metabolized in the liver mainly by CYP3A4, with less than 10% of the dose excreted in urine unchanged. Further, tamsulosin is extensively bound to human plasma proteins (94% to 99%), primarily $\alpha_1$-acid glycoprotein (AGP) [11].

## Methods

### Clinical studies

An overview of the clinical studies data used for model development and for evaluation of model-based predictions is displayed in Table 6.1. The comprehensive descriptions of the designs of these studies and the results have been reported elsewhere [12]. All data was collected following

administration of modified released capsules of tamsulosin. In total, the data of 14 healthy male adults from two phase I clinical studies (study 1 and 2) were used for model development. The data from 8 patients with hepatic impairment (study 2), 12 patients with renal impairment (study 1) and 98 pediatric patients with symptoms of dysfunctional voiding (study 3) were exclusively used to verify the model-based predictions. Patients with hepatic impairment were classified as type A in the Child Pugh category and patients with renal impairment were classified as moderate (GFR≥30 and <70 mL/min) or severe (GFR>10 and GFR<30 mL/min). In all studies Tamsulosin concentrations in plasma were analyzed using liquid chromatography/mass spectrometry (HPLC) with a limit of quantification of 1.22 nmol/L, while tamsulosin hydrochloride concentrations in urine were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a limit of quantification of 0.244 nmol/L in study 1 and 0.187 nmol/L in study 2. In study 1 and 2, prior to the administration of tamsulosin, the free-fraction in plasma ($f_u$) was determined *in vitro* for each subject. All protocols were reviewed and approved by an independent ethics committee and a written informed consent was obtained from each subject prior initiation of the study.

**Table 6.1 Overview of the clinical studies used for model development and for evaluation of model-based predictions**

| Study number | Study description | Population | Treatment schedule | Dosage[e] | No. of subjects | Sampling scheme | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | Open label | Healthy subjects[a]; Patients with moderate or severe renal disease[b,c] | Single oral dose | 0.4 mg (fast) | 18 (6/6/6) | Plasma: 0.5, 1, 2, 3, 5, 6, 8,10, 12, 16, 20, 24, 30, 36, 48 and 72 h post-dose<br>Urine: 0-12, 12-24, | Miyazawa, 2001, 62: 603 |
| 2 | Open label, tolerability and pharmacokinetics | Healthy subjects[1]; Patients with hepatic impairment[b,d] | Single oral dose | 0.4 mg (fast) | 16 (8/8) | Plasma: 0.5, 1, 2, 3, 5, 6, 8,10, 12, 16, 20, 24, 30, 36, 48 and 72 h post-dose<br>Urine: 0-12, 12-24, | Miyazawa, 2001, 62: 603 |
| 3 | Double blind, pharmacokinetics, safety, tolerability and efficacy | Pediatric patients (6 - 12 years) with signs and symptoms of dysfunctional voiding[2] | Multiple oral dose | 0.1, 0.2 and 0.4 mg (after breakfast) | 98 | Plasma at steady state: trough, 1-4 h and 6-10 h post-dose | Not published |

[a]data used for model development; [b]data used for comparison with model predictions; [c]renal function was based on creatinine clearance and defined as moderately ($30 \leq GFR < 70$ mL/min/1.73m$^2$) and severely impaired ($10 < GFR < 30$ mL/min/1.73m$^2$); [d]liver function classified using Child-Pugh score A (6 out of 8 patients) and B (2 out of 8 patients). Patients with Child-Pugh score B were excluded from the comparisons (too few patients); [e]modified release formulation form of tamsulosin was administered to all patients

## Structural model

### *Semi-physiological pharmacokinetic model*

The pharmacokinetics of tamsulosin in plasma was described by a two compartment model with first-order absorption. The central compartment was assumed to be composed of multiple components that are in instantaneous equilibrium: tamsulosin-AGP, tamsulosin-free and tamsulosin-

non-specific binding (NSB). To describe the central volume of distribution (V1) the following equation was derived:

$$V_1 = V_{plasma} \cdot (1 + \beta \cdot f_u) \quad \text{Equation 6.1}$$

where $V_{plasma}$ is the volume of plasma in L calculated as 5 percent of the lean body mass [13, 14], β is a compilation of the concentration in the NSB divided by the partition coefficient for NSB and $f_u$ is the free fraction in plasma individually measured and whenever missing, calculated using Equation 6.2.

$$f_u = \frac{1}{1 + \frac{C_{AGP}}{k_{AGP}}} \quad \text{Equation 6.2}$$

in which CAGP is the measured AGP-plasma concentration in nmol/L, and kAGP is the partition coefficient for AGP also in nmol/L.

The volume of distribution at steady state (VSS) was included into the model using the same physiological equation as for solifenacin [15, 16]:

$$V_{ss} = V_{plasma} + V_{water} \cdot \left( \frac{f_u}{f_{tissue}} \right) \quad \text{Equation 6.3}$$

in which $f_{tissue}$ is the estimated free fraction in tissue and $V_{water}$ is calculated the aqueous volume in L outside of the plasma into which the drug distributes [17]. The $V_{water}$ was assumed to be total body water composition minus plasma water volume, which is approximately 90% of $V_{plasma}$. Total body water composition was calculated according to Watson et al [18].

In order to allow renal clearance ($CL_R$) and hepatic clearance ($CL_H$) to be individually estimated, urine concentrations were also described in the model by linking a urine compartment to the central compartment. Hence, total clearance (CL) was determined as follows

$$CL = CL_H + CL_R \quad \text{Equation 6.4}$$

Renal clearance was characterized as a fraction of the clearance due to the glomerular filtration rate ($CL_{GFR}$) as displayed in Equation 6.5.

$$CL_R = \alpha \cdot CL_{GFR}$$
$$CL_{GFR} = GFR \cdot f_u \quad \text{Equation 6.5}$$

where $\alpha$ is a fraction of CLGFR. If $\alpha$ >1, tubular active secretion contributes to renal clearance; if $\alpha$ <1 reabsorption is predominant in renal clearance; and if $\alpha$ =1 GFR suffices to describe renal clearance. GFR was calculated according to the modification of diet in renal disease (MDRD) equation [19] and corrected for body surface area (BSA) [20]. The hepatic clearance was characterized by using a well-stirred model according to equation Equation 6.6 [21].

$$CL_H = \frac{Q_H \cdot f_u \cdot Cl_{int\,rinsic}}{Q_H + f_u \cdot \frac{Cl_{int\,rinsic}}{RB}}$$ Equation 6.6

where $Q_H$ was calculated according to Wynne et al [22]; RB is total blood to plasma concentration ratio assumed to be one and to remain constant under all the (patho-)physiological conditions investigated; and $CL_{intrinsic}$ is intrinsic clearance which was calculated as follows:

$$CL_{int} = CL_{invivo} \cdot LiverWeight \cdot MPPGL$$ Equation 6.7

where $CL_{invivo}$ is the *in vivo* clearance, liver weight was calculated according to Chouker *et al* [23] and MPPGL is the milligrams of microsomal protein per gram liver which adult levels were reported as 35 mg/g [24].

The inter-compartmental clearance was multiplied by free fraction and blood flow of well perfused tissues (e.g. lung, kidney and liver). Further, the maximal oral bioavailability ($F_{max}$) was physiologically characterized in this model as described in Equation 6.8

$$F_{max} = \frac{Q_H}{Q_H + CL_{int} \cdot \frac{f_u}{RB}}$$ Equation 6.8

### *Allometric scaling pharmacokinetic model*

For comparison purposes, parallel to the development of a semi-physiological pharmacokinetic model, an allometric scaling model was developed. Briefly, a two compartment model with first-order absorption was used to describe the pharmacokinetics of tamsulosin in plasma. Urine and free fraction data was not incorporated into the model. Further, a 0.75 allometric relationship was assumed between body weight and clearance and a linear relationship was assumed between body weight and volume of distribution.

### Random effects

Random inter-individual variability on each pharmacokinetic parameter was described as a log-normal distribution (Equation 6.9).

$$P_i = P_{typical} \cdot exp(\eta_i)$$ Equation 6.9

where $P_i$ represents the parameter value for the $i^{th}$ individual, $P_{typical}$ is the parameter for a typical group value and $\eta$ is the inter-individual random effect with $\eta_i \sim N(0, \varpi^2)$.

The residual errors were separately defined for tamsulosin concentrations in plasma and in urine:

$$C_{obs,ij} = C_{pred,ij} \cdot (1 + \varepsilon_{ij})$$ Equation 6.10

where $C_{obs,ij}$ and $C_{pred,ij}$ are respectively the observed concentration and the predicted concentration in individual i at time j and $\varepsilon_{ij}$ is the residual error with $\varepsilon_i \sim N(0, \sigma^2)$.

### Model performance

Throughout model development NONMEM subroutine ADVAN6 and first order conditional estimation with interaction was used. Samples below limit of quantification were considered as missing values. Model performance was evaluated by both visual inspection and likelihood ratio test. Physiological considerations and the conventional critical values for the likelihood ratio test ($p<0.001$) were used for model development. Precision of parameter estimates was evaluated as coefficient of variation (CV) calculated by the ratio of the estimated standard error and its respective parameter estimate multiplied by 100.

### Model evaluation

Internal model validation was performed by means of a visual predictive check, which evaluates (i) whether the semi-physiological pharmacokinetic model is able to predict the observed total plasma concentrations and urine excretion rates and; (ii) whether the allometric scaling model is able to predict the observed total plasma concentrations [25]. Simulations were performed for 1000 hypothetical subjects using the observed demographics. In all simulations, a correlation matrix for theta estimates was considered to account for parameter uncertainty. For the semi-physiological pharmacokinetic model, simulations were performed considering differences in the physiological parameters alone and combined with the estimated inter-individual variability for the allometric scaling model. For graphical representation of the urine data, the urinary excretion rate was calculated by dividing the simulated amount of total-tamsulosin excreted in the urine during a certain time-interval by the time interval.

### Extrapolations

The semi-physiological pharmacokinetic model was used to predict the pharmacokinetics of tamsulosin from healthy adults to hepatic and renal impaired patients and to pediatric patients. In pediatric patients, the predictions using the semi-physiological pharmacokinetic model were compared with the predictions using the allometric scaling model. The predictions using the semi-physiological pharmacokinetic model were exclusively based on alterations of various physiological parameters while the predictions using the allometric scaling model were exclusively based on the alterations in body weight. The physiological values of the parameters in hepatic and renal impaired patients were calculated on the basis of anthropometric equations and a factor to account for the expected differences, while in pediatric patients, $P^3M^{TM}$ were used to sample all required physiological parameters, except for AGP plasma concentrations [5], BSA [20], total body water [26] and glomerular filtration rate [20] (Table 6.2). Both model-based predictions in pediatric patients considered a factor 0.7 on the absorption rate constant and on the bioavailability in order to account for the food effect which was not considered in the adult model, where all data was obtained under fast conditions [11]. When using the semi-physiological pharmacokinetic model, the inter-compartmental clearance was considered relative to changes in the blood flow of well perfused tissues.

**Table 6.2 Overview of the expected changes in the physiological parameters in hepatic and renal impaired patients expressed as a fraction of the values in healthy subjects and in children expressed as a continuous age-related change**

| Physiological parameters | Hepatic impaired[a] [3] | Renal impaired [4] | Children |
|---|---|---|---|
| BSA | 1 | 1 | Anthropometric equation [20] |
| GFR | 1 | uniform distribution according to classification as specified in the protocol | Anthropometric equation [27] |
| $C_{AGP}$ | 0.60 | 1.4 (severe)<br>1.1 (moderate) | Anthropometric equation [24] |
| $V_{plasma}$ | 1 | 1 | P³M™ [28] |
| $V_{water}$ | 1 | 1 | P³M™ [28] |
| $Q_H$ | 0.63 | 1 | P³M™ [28] |
| Liver weight | 0.69 | 1 | P³M™ [28] |
| $CL_{int}$ | 1 | 1 | Maturation function of CYP3A enzyme activity [10] |
| $Q_{well\ perfused\ tissues}$ | 1 | 1 | P³M™ [28] |

[a]Physiological changes associated with Child-Pugh score A; P³M™: Physiological Parameters for PBPK Modeling™ software. Abbreviations: BSA is the body surface area, GFR is the glomerular function ratio, $C_{AGP}$ is the AGP-concentration, $V_{plasma}$ is the volume of plasma, $V_{water}$ is the aqueous volume outside of the plasma, $Q_H$ is the liver blood flow, $CL_{int}$ is the intrinsic clearance and $Q_{well\ perfused\ tissues}$ is the blood flow of well perfused tissues.

Model-based predictions were compared with the observed data by means of a visual predictive check of the full pharmacokinetic profiles and by means of a posterior predictive check on the volume of distribution, clearance, area under the curve and half-life. A separate visual and posterior predictive check was performed for each (patho-)physiological condition evaluated. In the visual predictive check, 1000 concentration time profiles were simulated. The calculated median and 90% population predictions were compared against the observed concentration time data. For the posterior predictive check, 1000 data sets were simulated containing the same number of individuals as observed in the original data set. All individual pharmacokinetic parameters simulated from each data set provided a median and from all 1000 medians the 95% confidence interval was calculated. These values were compared against the median of the observed pharmacokinetic parameters originated from a post-hoc analysis. In the posterior predictive check the observed AGP concentrations were used for the predictions in hepatic and renal impaired patients.

## Simulations

The semi-physiological pharmacokinetic model and the allometric scaling model were used to predict the volume of distribution, clearance and half-life in infants (1 - 5 years), children (6 -11 years) and adolescents (12 – 18 years). Lower age groups were not investigated as allometric scaling alone is known not to be accurate in these age groups. Differences between the two models were investigated for population predictions and inter-individual variability. The inter-individual variability in the semi-physiological pharmacokinetic model was defined as the variability in the calculated

physiological parameters plus the model estimated variability, whereas the inter-individual variability in the allometric scaling pharmacokinetic model was defined as the variability in weight plus the model estimated variability.

### Software

Nonlinear mixed effect modelling was implemented using NONMEM version 7.1.0 (GloboMax, Ellicot City, Maryland, USA). Data management and simulations were performed using R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) in combination with RStudio™ version 0.98.501 (RStudio, Inc., Boston, Massachusetts, USA). Some of the physiological parameters in children were derived using $P^3M^{TM}$ version 1.3 (The Lifeline Group, Annandale, Virginia, USA) [28].

## Results

### Data

An overview of the demographic and the derived physiological parameter estimates is displayed in Table 6.3. In adults, the demographics were comparable between the different groups except for the moderate renal impaired patients who were slightly older than the other groups. The physiological parameters for the hepatic and renal impaired patients were considered to be different by applying the factor as displayed in Table 6.2. In healthy adults, the median measured AGP-plasma concentrations ($C_{AGP}$=58 mg/dL) were found to be a factor 0.7 of the values normally observed ($C_{AGP}$~79.5 mg/dL) [4], presumably because of inter-laboratory and inter-assay variability. As a result, the same factor had to be applied to the values of AGP-plasma concentrations calculated for the pediatric patients. After correction, the median AGP-plasma concentrations calculated in children ($C_{AGP}$=58 mg/dL) were similar to the observed the AGP-plasma concentrations in healthy adults (as expected) and in children ($C_{AGP}$=61 mg/dL) (Table 6.3). The calculated fractions of adult values of the intrinsic clearance were shown to be close to 1.

**Table 6.3 Summary statistics (median and range) of the demographics and physiological parameters in different subpopulations**

| Demographics/ Physiological parameter | Control (healthy adults) n=13 | Hepatic impaired[a] n=5 | Renal impaired (Moderate)[b] n=6 | Renal impaired (Severe)[c] n=6 | Children n=98 |
|---|---|---|---|---|---|
| Age (years) | 50 (31 - 73) | 56 (42 - 61) | 66 (38 - 70) | 50 (29 - 58) | 9 (6 - 12) |
| Weight (kg) | 87.2 (61.5 - 106) | 73.2 (68.6 - 87.7) | 81.9 (70.7 - 107) | 76.9 (56.5 - 109) | 30 (18 - 59) |
| BSA ($m^2$) | 2.11 (1.71 - 2.4) | 1.87 (1.80 - 2.11) | 2.02 (1.86 - 2.37) | 1.97 (1.64 - 2.40) | 1.06 (0.758 - 1.60) |
| LBM (kg) | 63.1 (50.8 - 76.7) | 54.8 (53.3 - 64.9) | 61.5 (56.2 - 73.6) | 59.2 (48.7 - 74.9) | NA[e] |
| GFR ($mL/min/1.73m^2$) | 111 (90.7 - 144) | 126 (83.4 - 181) | 59 (36.5 - 63.1) | 14 (8.20 - 16.3) | 127 (92.3 - 174)[f] |
| $C_{AGP}$ (mg/dL) | 58.0 (36.7 – 70.0) | 40.5 (26 - 65) | 83.0 (54.0 – 98.0) | 71.5 (63.0 – 96.0) | 60.7 (36.8 - 119)<br>58.2 (57.2 - 58.7)[d] |

| | | | | | |
|---|---|---|---|---|---|
| $V_{plasma}$ (L) | 3.55 (2.86 - 4.31) | 3.08 (3.00 - 3.65)[d] | 3.46 (3.16 - 4.13)[d] | 3.33 (2.74 - 4.21)[d] | 0.74 (0.343 – 2.59)[f] |
| $V_{water}$ (L) | 42.9 (35 - 49.8) | 36.8 (35.4 - 43.3)[d] | 39.3 (37.5 - 48.5)[d] | 40.2 (34.8 - 50.5)[d] | 12.1 (5.26 – 50.5)[f] |
| $Q_H$ (L/h) | 117 (79 - 142) | 61.7 (57.8 - 73.9)[d] | 90.5 (74.8 - 137)[d] | 103 (79.3 - 146)[d] | 36.9 (19.2 - 113)[f] |
| Liver weight (g) | 2150 (1750 - 2740) | 1230 (1180 - 1700)[d] | 1940 (1760 - 2710)[d] | 2080 (1720 - 2830)[d] | 677 (350 - 1670)[f] |
| $CL_{int}$ (fraction of healthy adult values) | 1 | 1 | 1 | 1 | 0.973 (0.781 – 1.00)[f] |
| $Q_{well\ perfused\ tissues}$ (fraction of healthy adult values) | 1 | 1 | 1 | 1 | 0.565 (0.375 – 0.980)[f] |

[a]Only patients with Child-Pugh score A (too few patients with score B); [b]30≤GFR<70 mL/min/1.73m$^2$; [c]10<GFR<30 mL/min/1.73m$^2$; [d] physiological values calculated considering the differences as stated in Table 6.2; [e]not applicable to the anthropometric equations in children; [f]could not be individually calculated because individual values were lacking in the data set. P$^3$M database was used to derive these physiological parameters. Abbreviations: BSA is the body surface area, LBM is the lean body mass, GFR is the glomerular function ratio, $C_{AGP}$ is the AGP-concentration, $V_{plasma}$ is the volume of plasma, $V_{water}$ is the aqueous volume outside of the plasma into which the drug distributes, $Q_H$ is the liver blood flow, $CL_{int}$ is the intrinsic clearance and $Q_{well\ perfused\ tissues}$ is the blood flow of well perfused tissues.

## Final models

The final semi-physiological pharmacokinetic model to describe the pharmacokinetics of tamsulosin in healthy adults is illustrated in Figure 6.1. During model development, the non-specific binding (NSB) in the central compartment outside of the plasma and in instantaneous equilibrium with the other components, was found to be negligible, since the concentration in the NSB divided by the partition coefficient for NSB (β) was found to be zero. As a result, V1 was found to be equal to the volume of plasma ($V_{plasma}$) and independent of fu. Additionally, the $k_{AGP}$ could not be estimated as fu was missing for one healthy adult. Therefore, the value of $k_{AGP}$ was fixed to the value of 136 nmol/L, which was calculated using Equation 6.2.

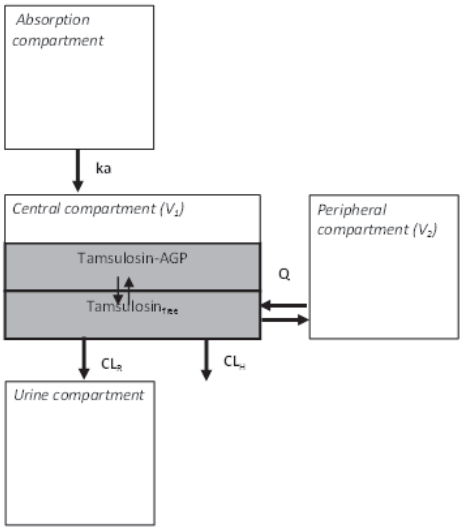


**Figure 6.1 Schematic representation of the semi-physiological pharmacokinetic model developed for tamsulosin. The arrows within the central compartment represent instantaneous equilibrium and arrows between compartments represent kinetic processes. Total plasma concentrations, plasma-protein concentrations and individual free fractions were measured in the compartments indicated by the bold lines and grey color. The urine concentration was measured in the compartment named urine.**

The adequacy of the semi-physiological pharmacokinetic model and of the allometric scaling model to describe the observed plasma concentrations and when applicable the observed urinary excretion rates were illustrated by means of visual predictive checks in Figure 6.2. The population predictions of the plasma concentration-time profiles for both models were shown comparable. The inter-individual variability, however, seemed to be slightly over-predicted by the allometric scaling pharmacokinetic model especially in the later time points (time>30 h). For the semi-physiological pharmacokinetic model, the visual predictive check also illustrated that considerable part of the inter-individual variability could be explained by considering only the variability in the physiological parameters, i.e. without random-effect (inner shade).

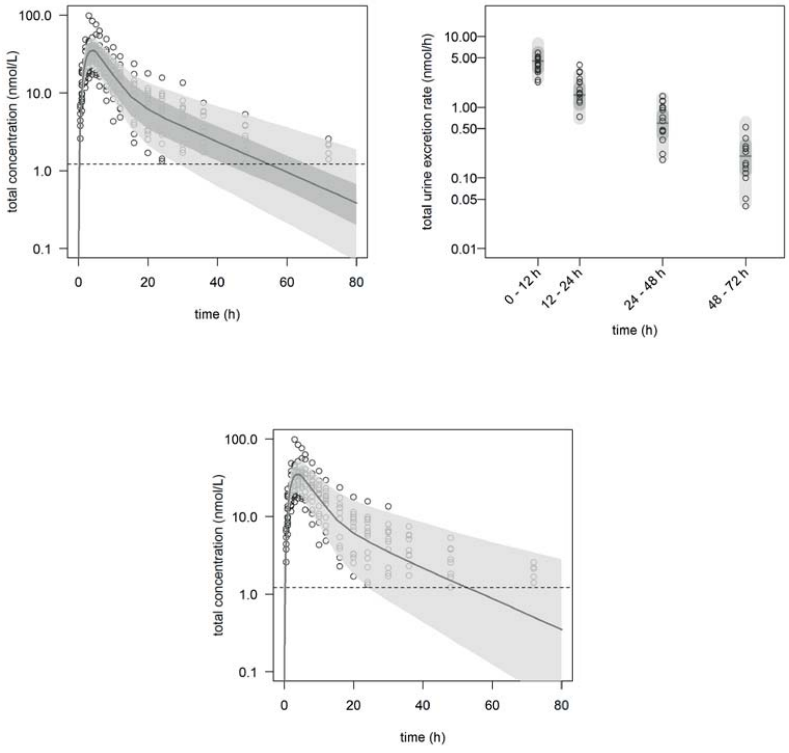


**Figure 6.2 Internal visual predictive check of the total tamsulosin plasma concentrations and urine excretion rate after single dose administration of 0.4 mg of tamsulosin in healthy volunteers. Upper row show the results for the semi-physiological pharmacokinetic model and the lower row shows the results for the allometric scaling model. Open circles: observed data of study 1 and 2; line: population prediction (median); inner shade: 90% predicted population variability explained by the differences in the physiological parameters; outer shade: 90% predicted population variability including differences in the physiological parameters and random-effects.**

The values of i) the model parameter estimates and the derived structural parameters of the semi-physiological pharmacokinetic model and ii) the population parameter estimates using allometric scaling model are depicted in Table 6.4. All structural parameters from both models were estimated with good accuracy (similar between the two models) and good precision (CV<29 % for the semi-physiological pharmacokinetic model and CV<12 % for the allometric scaling model). The highest difference was observed for the central volume of distribution where the value in the allometric scaling model ($V_1$=1.88 L) which was a factor 0.6 of the value of the semi-physiological pharmacokinetic model ($V_1$=2.94 L). For both models, the inter-individual variability was estimated for central volume of distribution and (hepatic and renal) clearance. Correlation between inter-individual variability of central volume of distribution and (hepatic and renal) clearance was accounted for using an omega matrix. No relevant shrinkage in the omega distribution was observed (12.7% for $V_1$, -3.05% for $CL_H$ and 5.37% for $CL_R$ for the semi-physiological pharmacokinetic model and; 19.5% for V1 and 3.04% for $CL_H$ for the allometric scaling model). The residual errors were also similar in both models (0.0431 for the semi-physiological pharmacokinetic model and 0.0505 for the allometric scaling model).

**Table 6.4 Population parameter estimates including coefficient of variation (CV%) and median of the derived structural parameters including range (minimum-maximum)**

| | **Semi-physiological pharmacokinetic model** | **Allometric scaling pharmacokinetic model** |
|---|---|---|
| *Structural estimated parameters* | *Value (CV %[d])* | *Value (CV %[d])* |
| ka (/h) | 0.404 (5.0) | 0.365 (7.9) |
| $Cl_{in\ vivo}$ (L/h/g liver protein) | 0.00238 (12) | |
| $\alpha$ | 2.53 (12) | |
| $Q^*$ (L/h) | 184 (11) | |
| ß[a] | 0 (fixed) | |
| $f_{tissue}$ | 0.0219 (7.4) | |
| $k_{AGP}$ (nmol/L)[b] | 136 (fixed) | |
| *Structural (derived) parameters[c]* | *Median (range)* | |
| $F_{max}$ | 0.983 (0.977 - 0.986) | |
| $V_1$ (L) | 2.94 (1.84 - 5.85) | 1.88 (29) |
| $V_2$ (L) | 19 (14.2 - 31.5) | 17 (8.1) |
| $V_{SS}$ (L) | 23.5 (16.0 - 35.5) | |
| CL (L/h) | 1.94 (0.830 - 5.18) | 1.74 (14) |
| $CL_H$ (L/h) | 1.78 (0.725 - 4.46) | |
| $CL_R$ (L/h) | 0.178 (0.105 - 0.716) | |
| Q (L/h) | 1.89 (1.57 – 2.96) | 1.79 (11.0) |
| $f_u$ | 0.0102 (0.0085 – 0.0161) | |
| *Random inter-individual variability* | *Value (CV %[d])* | |
| $\omega^2 V_1$ | 0.165 (49) | 0.117 (52) |
| $\omega^2 CL_H$ | 0.148 (30) | |
| $\omega^2 CL_R$ | 0.121 (67) | |
| $\omega^2$ CL | | 0.242 (30) |
| *Residual error* | *Value (CV %[d])* | |
| $\sigma^2$ plasma | 0.0431 (11) | 0.0505 (12) |
| $\sigma^2$ urine | 0.092 (24) | |

[a]$V_{plasma}$ was found to be equal to $V_1$; [b]Calculated based on equation only for the subjects were $f_u$ was not available; [c]parameters were derived for the semi-physiological pharmacokinetic model and estimated for the allometric scaling model; [d]precision in which parameters are calculated by the models.

## Extrapolations

First, model-based predictions were evaluated for hepatic and renal impaired patients. The evaluation for the full pharmacokinetic profile predictions by means of a visual predictive check is shown in Figure 6.3. Adequate model-based predictions were observed for all patient groups, except for a slight under-prediction in patients with moderate renal impairment.

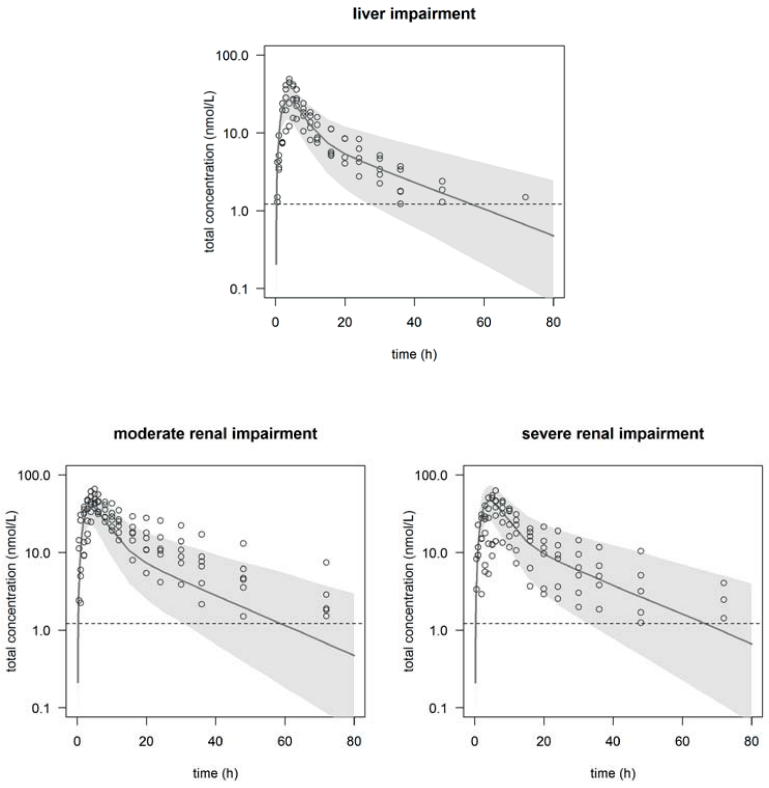


**Figure 6.3 Extrapolation of plasma concentration from healthy volunteers to patients with hepatic (upper panel) and renal impairment (lower panels). Open triangles: observed data study 1 and 2; line; population prediction (median); shade: 90% including differences in the physiological parameters and random-effects.**

The results of the posterior predictive check shown in Table 6.5 were accurate for prediction of the pharmacokinetic parameters in hepatic and renal impaired patients. Slight over-prediction of the renal clearance in patients with severe renal impairment was shown to be irrelevant for the prediction of the total clearance. The limited number of observed data hampered evaluation of accuracy of the predictions of the inter-individual variability.

**Table 6.5 Posterior predictive check for volume of distribution ($V_{SS}$), clearance (CL), renal clearance ($CL_R$), area under the curve ($AUC_{inf}$) and terminal half-life ($t_{1/2}$) in various pathological conditions. For every pharmacokinetic parameter the**

median observed values (post hoc analysis) and the simulated 95% population prediction of the posterior distribution (N=1000).

| Pharmacokinetic parameter | Control (healthy adults) | Hepatic impaired[1] | Renal impaired (Moderate[2]) | Renal impaired (Severe[2]) |
|---|---|---|---|---|
| $V_{SS}$ (L) | 23.5 (20.5 - 28) | 32.8 (20.1 - 46.4) | 21.6 (15.7 - 21.8) | 21.3 (15.3 - 26.5) |
| CL (L/h) | 1.94 (1.59 - 2.77) | 2.48 (1.19 - 3.76) | 1.05 (0.94 - 1.95) | 1.32 (0.988 - 2.33) |
| $CL_R$ (L/h) | 0.178 (0.157 - 0.278) | 0.379 (0.164 - 0.68) | 0.0917 (0.0452 - 0.113) | 0.0298 (0.0104 - 0.0295) |
| $AUC_{inf}$ (ng/mL.h) | 206 (144 - 252) | 162 (106 - 337) | 380 (206 - 432) | 304 (175 - 411) |
| AUC ratio | NA | 0.783 (0.474 - 2.10) | 1.84 (0.868 - 2.60) | 1.47 (0.804 - 2.47) |
| $t_{1/2}$ (h) | 14.7 (13 - 17) | 15.2 (13.3 - 21.2) | 19.1 (13.2 - 19.1) | 15.1 (12.9 - 19) |

[1] Only patients with Child-Pugh score A; [2] 30≤GFR<70 mL/min/1.73m$^2$; [3] 10<GFR<30 mL/min/1.73m$^2$; NA: not applicable

Next, model-based predictions were evaluated in pediatric patients from 6 to 12 years. The evaluation of the full pharmacokinetic profile predictions by means of a visual predictive check are shown in Figure 6.4 for both semi-physiological and allometric scaling pharmacokinetic model. Population predictions were accurate and comparable for both models, but a comprehensive evaluation was limited by the short sampling time. The inter-individual variability predictions were under-predicted in the absorption phase by both models and slightly over-predicted at the terminal phase by the allometric scaling model.

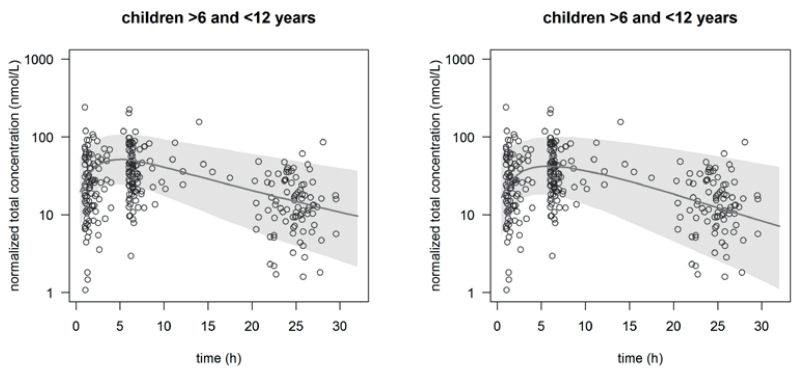


Figure 6.4 Extrapolation of plasma concentration from healthy adults to children from 6 to 12 years old. Left panel: extrapolation using the allometric scaling pharmacokinetic model; right panel: extrapolation using the semi-physiological pharmacokinetic model. Open circles: observed data normalized to administered dose in study 3; line; population prediction (median); shade: 90% including differences in the physiological parameters and random-effects.

The results of the posterior predictive check in Table 6.6 showed that volume of distribution was slightly over-predicted when the semi-physiological pharmacokinetic model was used and that the area under the curve and the half-life were respectively over and under-predicted when the allometric scaling model was used.

Table 6.6 Posterior predictive check for volume of distribution ($V_{SS}$/F), total clearance (CL/F), area under the curve ($AUC_{tau}$) and terminal half-life ($t_{1/2}$) in children. For every pharmacokinetic parameter the simulated median and the 95%

**population prediction of the posterior distribution (N=1000) are depicted using the semi-physiological and the allometric scaling pharmacokinetic model. The observed values were obtained based on a post hoc analysis using the allometric scaling model**

| Pharmacokinetic parameter | Children (observed) [1] | Children (semi-physiological) | Children (allometric scaling) |
|---|---|---|---|
| $V_{SS}/F$ (L) | 12.2 | 13.5 (12.4 - 14.7) | 11.6 (10.7 - 12.5) |
| CL/F (L/h) | 1.15 | 1.26 (1.11 - 1.41) | 1.33 (1.15 - 1.53) |
| $AUC_{tau}$ (ng/mL.h)[1] | 349 | 319 (284 - 359) | 300 (261 - 346) |
| $t_{1/2}$ (h) | 10.1 | 10.4 (9.63 - 11.1) | 8.95 (8.20 - 9.79) |

[1] Following administration of 0.4 mg of tamsulosin; Abbreviations: $AUC_{tau}$ is the area under the curve from time zero to tau where tau is the dosing interval

## Simulations

The simulations in children from 1 to 18 years are illustrated in Figure 6.5. The population predictions for volume of distribution were consistently slightly lower than for the semi-physiological pharmacokinetic model while the clearance and half-life predictions were sometimes lower and sometimes higher than for the semi-physiological pharmacokinetic model. The most evident differences were observed for the half-life predictions. The inter-individual variability predictions were similar for half-life but oppositely different for volume of distribution and clearance. The most marked differences in the inter-individual variability predictions were observed for the clearance in adolescents.

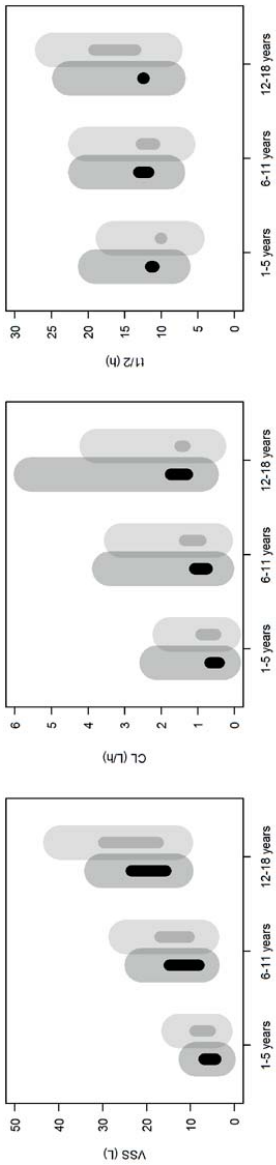


**Figure 6.5 Simulations from healthy adults to children comparing the predictions of $V_{SS}$/F, CL/F and terminal half-life using the allometric scaling (black) and the semi-physiological pharmacokinetic models (grey). Shade: 90% population prediction and; bars: range of the predictions considering only the differences in the physiological parameters.**

## Discussion

The proposed semi-physiological framework for the prediction of pharmacokinetics in special populations utilizes (i) a general partitioning framework to account for plasma-protein binding; (ii) key principles from physiology that apply to absorption, distribution, metabolism and excretion and; (iii) the power of the non-linear mixed effect modeling for estimation of population and random-effect parameters. Predictions using this approach only require adjustment of the physiological parameters that are known to change upon disease and/or growth. Recently, the applicability of the semi-physiological framework was demonstrated for prediction of the pharmacokinetics of solifenacin upon disease-related changes in hepatic and renal impaired patients [4]. In this investigation, the applicability of the semi-physiological framework was cross-evaluated to predict the pharmacokinetics of tamsulosin upon disease-related changes in hepatic and renal impaired patients, and also upon growth-related changes in children from 6 to 12 years. The predictions in children were placed into perspective by comparing the semi-physiological framework to the allometric scaling approach.

First, a semi-physiological pharmacokinetic model was developed to describe the pharmacokinetics of tamsulosin in healthy adults using rich clinical data (Table 6.1). For tamsulosin, the effect of non-specific binding on partitioning was estimated to be negligible and preservation of tamsulosin partitioning in the central compartment was limited to specific plasma protein binding (Figure 6.1). This model was shown to adequately describe the data (Figure 6.2) and the structural parameters (Table 6.4) were in agreement with the parameters obtained by non-compartmental analysis [11]. Also, the derived bioavailability was close to 100% (F=0.983) which was comparable to the bioavailability under fasted conditions observed in a clinical study [29]. The high bioavailability suggests that tamsulosin is only slightly affected by the first-pass metabolism in the liver. Further, the similarity between the measured $CL_{invitro}$ (0.00269 L/h/g liver protein) [30] and the estimated $CL_{invivo}$ (0.00238 L/h/g liver protein; Table 6.4) suggests that influx hepatic drug transporters do not play a role in the in vivo hepatic clearance of tamsulosin. To our knowledge, there are no in vitro studies demonstrating the influence of hepatic drug transporters. In general, these model results confirmed previous findings for solifenacin, showing that the semi-physiological framework aids to improve the understanding of the pharmacokinetic properties of the drug without affecting the adequacy of the data description and the accuracy/precision of the parameter estimates. In addition, the physiological features enable the extraction of physiological parameters that are directly impacted upon through disease and/or growth-related changes.

Next, the semi-physiological pharmacokinetic model was used to predict the pharmacokinetics in hepatic and renal impaired patients. Hence, literature reported physiological modifications in hepatic and renal impaired patients (Table 6.2) were applied to the physiological parameters as displayed in Table 6.3. On the contrary of solifenacin, intrinsic clearance of tamsulosin was assumed not to be affected by severe renal impairment [4]. This is in line with the original hypothesis that alteration in the intrinsic clearance of solifenacin in severe renal impaired patients was the result of alterations in the expression and function of hepatic uptake transporters caused by reduction of renal clearance and the consequent accumulation of uremic toxins [31, 32]. For tamsulosin, alterations in hepatic uptake transporters are not expected to impact the intrinsic clearance since hepatic drug transporters do not seem to play a role in the intrinsic clearance of tamsulosin (measured $CL_{invitro}$ ~ estimated $CL_{invivo}$).

All the physiological modifications in hepatic and renal impaired patients resulted in adequate prediction of the observed data (Figure 6.3; Table 6.5). Only for the moderate renal impaired patients, a slight under-prediction of the pharmacokinetic profiles was observed. This under-prediction is likely to be a consequence of higher observed AGP concentrations (Table 6.3) than expected based on literature values (Table 6.2). Higher AGP concentrations lead to lower free fraction which influences hepatic clearance and volume of distribution at steady state. The influence of AGP concentrations is supported by the accuracy of the posterior predictive check results which was performed using the observed instead of the predicted AGP concentrations (Table 6.5). Altogether, the results for the extrapolations from healthy adults to hepatic and renal impaired patients showed that the physiological features incorporated into the semi-physiological framework is sufficient to predict changes in the pharmacokinetics caused by disease.

Furthermore, the adequacy of the semi-physiological framework to predict the pharmacokinetics from adults to children between 6 and 12 years was also evaluated. The results showed the pharmacokinetic profiles in children to be well predicted at population and inter- individual variability level, except for the absorption phase which variability was clearly larger than observed in adults (Figure 6.4). Differences in absorption between adults and children are likely to be due to the less controlled setting of the pediatric study, especially with regard to the time of administration of the drug and the food status. The data in adults were under fast conditions, while in children were under uncontrolled fed condition (Table 6.1). This, however, did not impact the accuracy of the prediction of pharmacokinetic parameters (Table 6.6). The predicted value for clearance but not for volume of distribution were shown in agreement with estimated values based on a population pharmacokinetic model previously reported to describe pediatric data [33]. Differences in estimated volume of distribution (37.5 L/h - Tsuda et al. 2010- vs. 19 or 24 L/h) are likely to be attributed to the conduct of population pharmacokinetic analysis on sparse sampling data.

Finally, the evaluation of the predictions in children using the semi-physiological framework was placed into perspective by comparing it with the allometric scaling approach which is a frequently used approach in pediatric drug development [8]. Therefore, an allometric scaling model was developed using the same data in adults as used to develop the semi-physiological pharmacokinetic model. The allometric scaling model was shown to adequately describe the data at a population level but to slightly over-estimate the inter-individual variability (Figure 6.4). The over-estimation of the inter-individual variability is most probably caused by assuming standard values for the allometric exponents into the model, which requires the model to compensate for potential biases using random-effects. This slightly over-estimation of the variability was also observed when the model was used to predict the pharmacokinetic profiles in children (Figure 6.2). In the case of tamsulosin, fixation of the allometric exponent did not lead to a considerable increase in the estimation of the inter-individual variability. It is expected, however, that the greater the increase in the estimation of the inter-individual variability in adults, the greater the over-prediction of the inter-individual variability in children will be.

In general, the predictions using the semi-physiological pharmacokinetic model were shown to be visually comparable at a population level with the predictions using the allometric scaling model (Figure 6.4). Simulations were performed in order to gain further insight into the expected of differences in predictions of the pharmacokinetic parameters in infants (1-5 years), children (6-11 years) and adolescents (12-18 years) (Figure 6.5). These simulations confirmed differences in the

prediction of the average half-life and inter-individual variability on clearance. Additionally, the posterior predictive check showed that the predictions on the terminal half-life in children using the allometric scaling model were statistical significant different from the observed data and the prediction using the semi-physiological pharmacokinetic model (Table 6.6). These results are in agreement with previous investigations showing that the use of allometric scaling for prediction of reasonably accurate pharmacokinetic profiles is not always possible [34]. On the other hand, it should be stressed out that evaluation of the predictions on the terminal half-life is by some means restricted due to the short sampling time (Table 6.1).

Although the differences between the semi-physiological and allometric scaling pharmacokinetic models were small, in children younger than 1 year they are expected to be augmented as allometric scaling predictions are known to be inaccurate even when combined with maturation functions to account for developmental changes in early ages [10, 35]. Additionally, we consider the semi-physiological framework to be more promising as it is based on the well-stirred model which was previously shown to accurately predict the clearance of a wide range of compounds from neonates to adolescents [10]. Another advantage is that the semi-physiological framework allows considering not only the growth and developmental changes, but also the potential disease-related changes on the pharmacokinetics. Such predictions are crucial not only for pediatric dose selection but for the analysis of the clinical study results which requires the use of priors in order to distinguish growth-developmental changes from disease changes.

In summary, the semi-physiological framework was successfully evaluated for the predictions of the pharmacokinetic profiles of tamsulosin in hepatic and renal impaired patients and in children. Overall, this investigation provided evidence that the semi-physiological framework can be used to predict alterations in the pharmacokinetics resultant from disease or growth related changes. Predictions of the semi-physiological framework in children was, however, only slightly better than the allometric scaling. Notwithstanding, only the semi-physiological framework is suitable for predictions upon simultaneous disease and growth changes.

## Acknowledgments

The authors acknowledge John Meijer, M.Sc. for his assistance in understanding the clinical data. This work was performed within the framework of the Dutch Top Institute Pharma project D2-104. No source of funding was used to assist in the preparation of this study. Ms. Strougo, Dr. Yassen and Mr. Krauwinkel are employees of Astellas Pharma Europe. Dr. Freijer was an Astellas Pharma Europe employee at the time this investigation was designed and performed. Currently, Dr. Freijer is employed at Boehringer Ingelheim.

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