

PREDICTION OF FOOD EFFECT IN THE CHINESE POPULATION USING A PBPK MODEL DEVELOPED IN A EUROPEAN POPULATION



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Introduction

Physiologically based pharmacokinetic (PBPK) models combine *in vitro* and *in silico* drug-specific data with population-specific physiological data in order to predict the PK of drugs *in vivo*. Their physiologically based model structure facilitates the extrapolation of drug PK to populations other than those for which the model was originally built and qualified, via the modification of relevant physiological parameters. The ability to predict drug PK in other populations is desirable in order to aid in the design of bridging studies, to anticipate study inclusion criteria and dose selection. This approach was used for the Servier drug S1, for which two phase 1 clinical studies had been first carried out in European Caucasian subjects. A first in man study in Chinese subjects was subsequently planned, in which a potential food effect was tested on a limited number of subjects. As a borderline BCS Class 1/2 drug (based on *in vitro* solubility data), PBPK predictions of food effect were desirable to anticipate whether the expected S1 exposure in Chinese subjects in the presence of food would be within the drug's safety margin.

Objectives

- To develop and qualify a PBPK model for the Servier drug S1 in the European Caucasian population
- To simulate the PK of S1 in fasted Chinese subjects, and compare with the observed data from the Chinese clinical study
- To simulate the PK of S1 in fed Chinese subjects, and compare the predicted food effect with the observed food effect from the Chinese clinical study.

Methods

PBPK modelling software

- Simcyp Version 14

PBPK model for S1 – drug-specific input parameters

- Physicochemical – base (pKa 7.6, 5.7), lipophilic (logP ~3.5), low $f_{u,plasma}$ (~1%)
- Absorption – mechanistic (ADAM) model, P_{eff} predicted from Caco-2 P_{app} (high), *in vitro* solubility-pH profile (solubility values indicate borderline BCS class 1/2)
- Distribution – minimal 2-compartment PBPK model with distribution parameters obtained from the existing European Caucasian population PK model
- Elimination – *in vitro* hepatic CL_{int} predicted from bacosomes with an f_m CYP3A4 of 50%, and an f_m CYP2C8 of 50%, and negligible renal clearance

PBPK model building and qualification with European Caucasian population PK data

- The PBPK model was built using the drug-specific parameters listed above, and the model was qualified for the therapeutic dose, by comparing predicted plasma concentration-time profiles with *in vivo* plasma concentrations obtained from two Phase 1 clinical studies in European Caucasian subjects.
- Predicted PK parameters ($AUC_{t,ss}$, $C_{max,ss}$) were calculated by Simcyp. $AUC_{t,ss}$ was calculated using the linear up log down method, and $C_{max,ss}$ was obtained from the simulated concentration profiles using a sampling interval of 0.05h.
- Observed PK parameters at steady state were previously reported (in-house) values obtained via the existing population PK model.

Simulation of PK in the Chinese population (fasted state)

- For the simulations using the Chinese population, the Chinese population file within the Simcyp library was used without modification.
- The trial design of the Chinese Phase 1 study was simulated as closely as possible
- Predicted PK parameters ($AUC_{t,ss}$, $C_{max,ss}$) were calculated by Simcyp. $AUC_{t,ss}$ was calculated using the linear up log down method, and $C_{max,ss}$ was obtained from the simulated concentration profiles using a sampling interval of 0.05h.

Simulation of food effect in the Chinese population

- For the food effect simulations, the Chinese population within the Simcyp library was used unmodified, and the 'fed' option was selected in the trial design.
- The trial design of the food effect part of the Chinese Phase 1 study was simulated as closely as possible, and predicted PK parameters were obtained as described above.

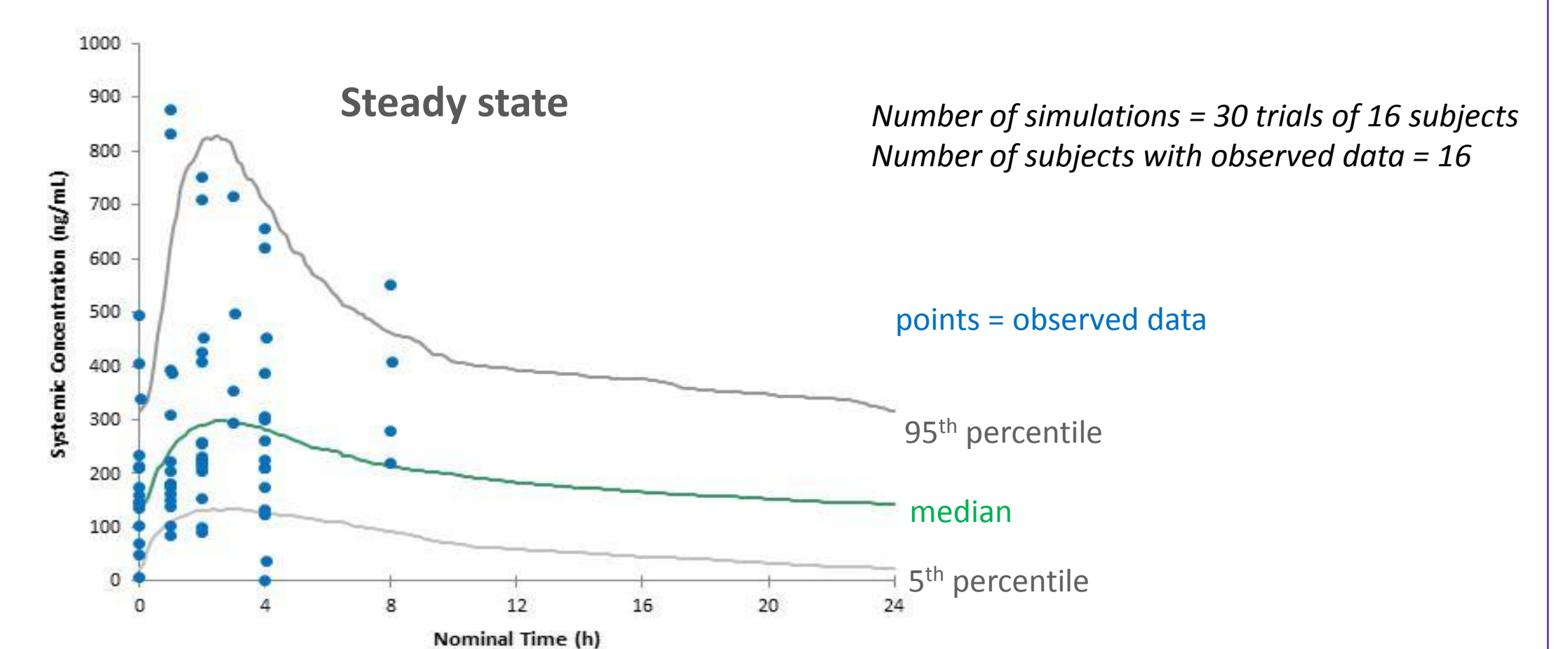
Observed data

- Observed PK parameters were calculated by noncompartmental analysis using the software WinNonlin Phoenix version 1.3.

Results

FASTED STATE – PREDICTION OF PK IN EUROPEAN CAUCASIAN SUBJECTS

Figure 1. Predicted vs observed S1 plasma concentration-time profiles for the North European caucasian population



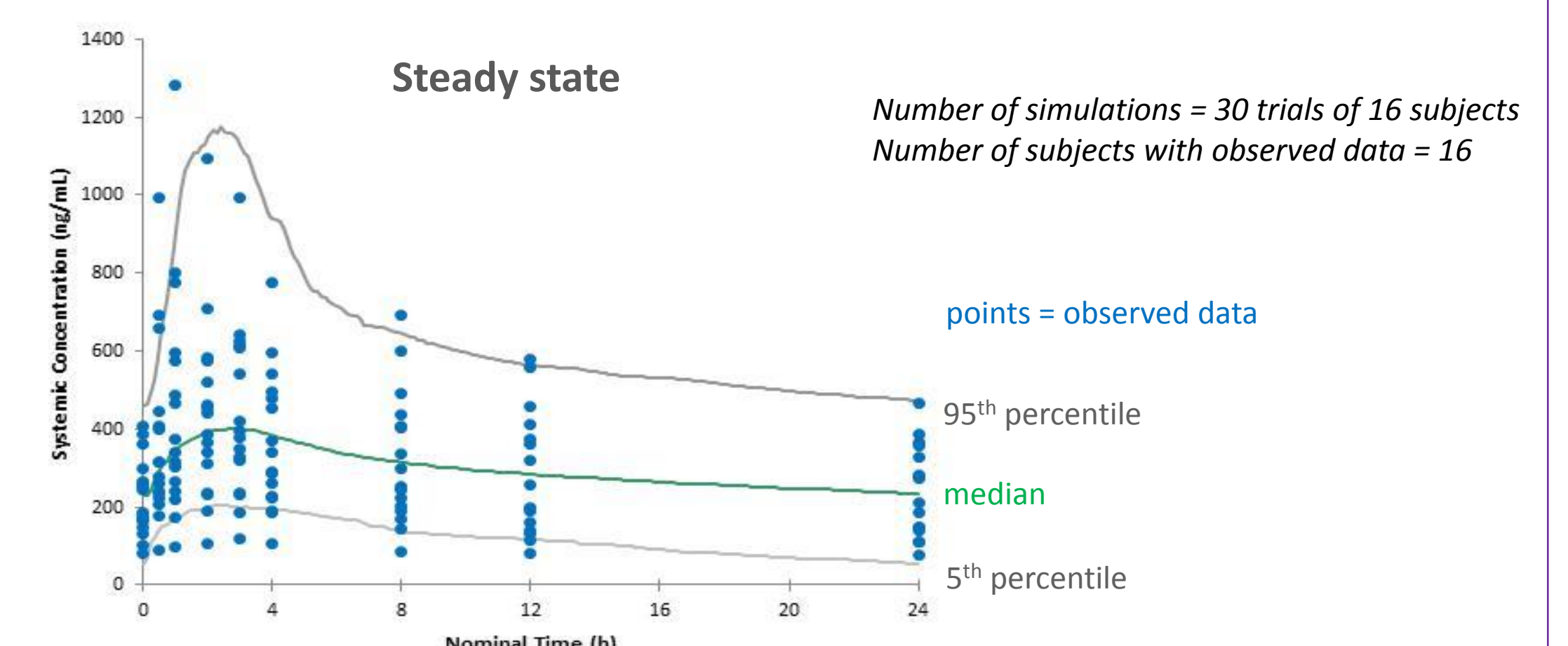
Parameter	$AUC_{t,ss}$ (h.ng/ml)	$C_{max,ss}$ (ng/ml)
Predicted	4818 [4604-5041]	315 [300-331]
Observed	4765 [3261-6960]	341 [251-464]

Predicted values are geometric mean of trial geometric means [90% confidence interval]
Observed values are geometric mean [90% confidence interval]

The PBPK model was qualified using the European Caucasian *in vivo* plasma concentration data and a good prediction of steady state $AUC_{t,ss}$ and $C_{max,ss}$ was obtained.

FASTED STATE – PREDICTION OF PK IN CHINESE SUBJECTS

Figure 2. Predicted vs observed S1 plasma concentration-time profiles for the Chinese population



Parameter	$AUC_{t,ss}$ (h.ng/ml)	$C_{max,ss}$ (ng/ml)
Predicted	7116 [6879-7361]	434 [416-453]
Observed	6441 [4804-8635]	435 [314-602]

Predicted values are geometric mean of trial geometric means [90% confidence interval]
Observed values are geometric mean [90% confidence interval]

A good prediction of steady state $AUC_{t,ss}$ and $C_{max,ss}$ was obtained in Chinese subjects in the fasted state. The predicted geometric mean steady state $AUC_{t,ss}$ and $C_{max,ss}$ ratios of Chinese-to-European subjects at this dose were 1.5 and 1.4, respectively, compared to the *in vivo* ratios of 1.4 and 1.3, respectively.

FOOD EFFECT PREDICTIONS IN CHINESE SUBJECTS

Number of simulations = 30 trials of 8 subjects
Number of subjects with observed data = 8

Parameter	$AUC_{t,ss}$	$C_{max,ss}$
Predicted food effect	1.05 [1.04-1.06]	1.04 [1.03-1.06]
Observed food effect	0.98 [0.90-1.06]	0.93 [0.79-1.10]

Food effect is defined as the PK parameter value in the fed state divided by fasted state
Predicted values are geometric mean of trial geometric means [90% confidence interval]
Observed values are geometric mean [90% confidence interval]

The predicted geometric mean steady state $AUC_{t,ss}$ and $C_{max,ss}$ fed-to-fasted ratios in Chinese subjects at the therapeutic dose were both 1.05 and 1.04, compared to the *in vivo* ratios of 0.98 and 0.93, respectively.

Conclusions

The $AUC_{t,ss}$ and $C_{max,ss}$ of the Chinese subjects in both fasted and fed conditions were well predicted by the PBPK model. Demographic differences, such as the lower abundance of CYP3A4 in Chinese patients versus Caucasians, and the smaller liver size of Chinese versus Caucasians, result in a lower hepatic clearance in Chinese patients. Demographic differences which affect absorption, and which were not taken into account in the model, may affect the fraction absorbed of S1. Nevertheless, a negligible food effect was predicted in the Chinese population using the PBPK model, and this was found to be in very good agreement with the observed data, which also showed a negligible food effect. This was due to the fact that the predicted fraction absorbed was high (over 95% absorbed) in the fasted state over the duration of the simulation, despite the relatively low *in vitro* solubility values. This shows the importance of dynamic predictions of absorption for drugs with *in vitro* solubility values which result in a borderline BCS classification, and of taking into account *in vitro* metabolism data and physiological differences in liver size and enzyme abundance for the *a priori* prediction of drug PK in the Chinese population.

References :

- Barter ZE, Tucker GT, Rowland-Yeo K. Differences in cytochrome P450-mediated pharmacokinetics between Chinese and Caucasian populations predicted by mechanistic physiologically based pharmacokinetic modelling. *Clin Pharmacokinet*. 2013. 52 : p. 1085-1100.
- Jamei M, Turner D, Yang J, Neuhoff S, et al. Population-based mechanistic prediction of oral drug absorption. *AAPS J*. 2009. 11 : p. 225-237.