

Alirocumab population pharmacokinetics in Chinese patients using priors

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Introduction

Alirocumab is a fully human monoclonal antibody directed against Proprotein Convertase Subtilisin Kexin type 9 (PCSK9), which is mainly expressed in the liver. PCSK9 directly binds to LDL-R (LDL-Receptor) and promotes LDL-R internalization and degradation. By blocking PCSK9 mediated regulation of LDL-R, alirocumab lowers serum LDL-C levels in a dose-dependent manner. Clinical studies did not evidence any impact of ethnicity on the pharmacokinetics of alirocumab. PRALUENT® (alirocumab) is currently approved in more than 60 countries worldwide, including Japan, Hong Kong and Taiwan, and has recently been submitted in China.

Objectives :

- Qualify a population pharmacokinetic (popPK) model for alirocumab in the Chinese population
- Compare alirocumab exposure parameters between Chinese and non-Chinese patients

Methods

The popPK model for total alirocumab (i.e., free and bound to PCSK9) displayed in Figure 1, which was previously developed on pooled clinical data of phase I, II and III studies (n patients ≈ 3000, mostly Caucasians) [1] was used for the analysis of a pooled dataset from phase I and III studies in Chinese patients (n = 68) using NONMEM prior's subroutine [2,3]. Chinese healthy volunteers (n=28) received a 75, 150 or 300mg single subcutaneous (SC) dose and Chinese high cardiovascular risk patients with hypercholesterolemia on background statin therapy (n=40) received an SC 75mg dose every 2 weeks (Q2W) over 24 weeks, with possible up-titration to 150mg Q2W at week 12.

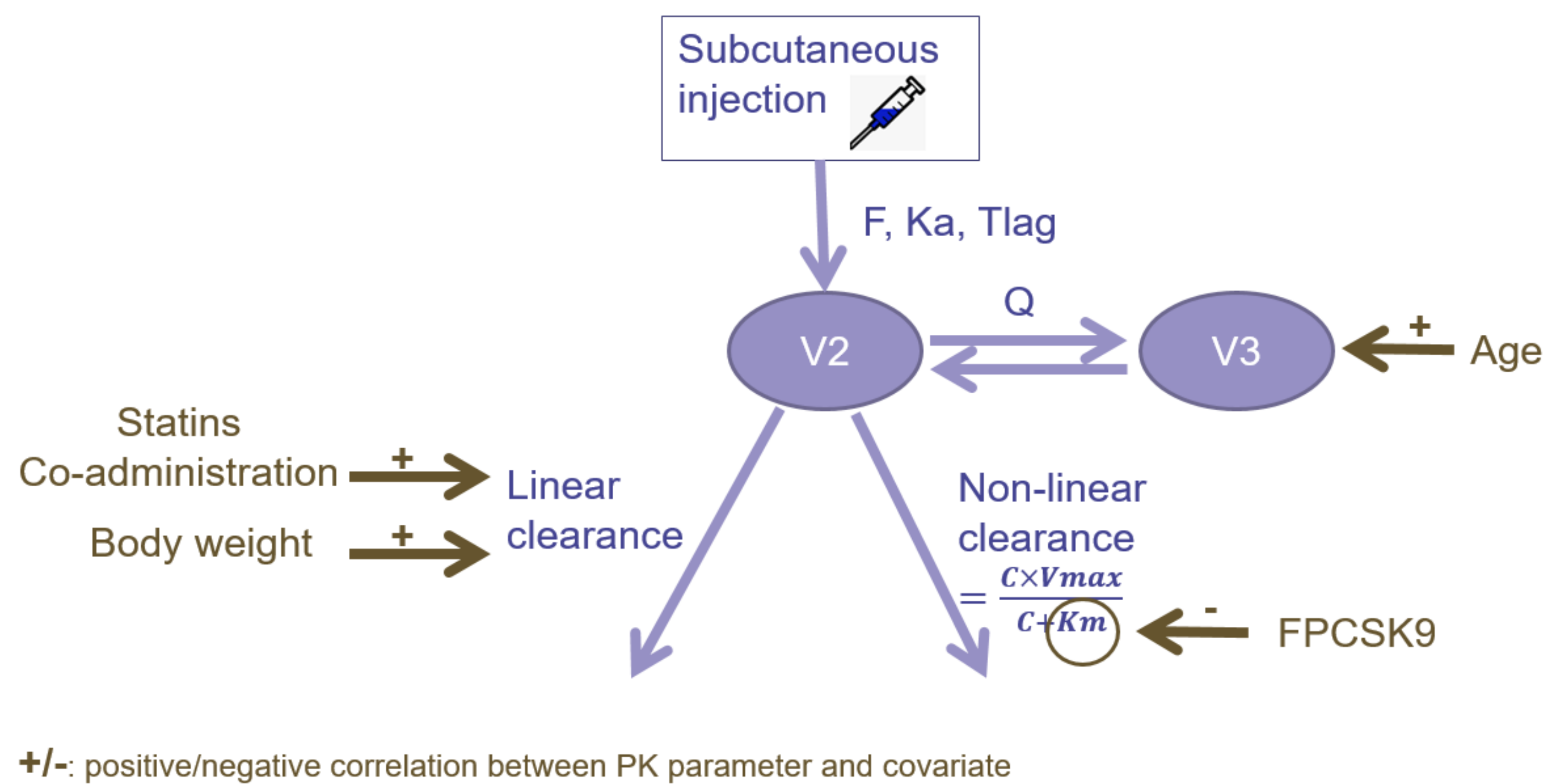


Fig. 1 Schematic of the previously developed final model.

Informative priors were first only used on bioavailability (structurally unidentifiable parameter). No priors were used for the remainder of the parameters. Informative priors were then iteratively added on parameters that were not precisely estimated or to stabilize minimization.

Model validation included goodness of fit plots, bootstrap, VPC with stratification on dose and clinical study and derivation of quality criteria using in-house tools [4]. The quality criteria were namely the average fold error (AFE), the root mean squared error (rmse%) and the mean prediction error (mpe%) expressed as percentage of mean concentrations.

Alirocumab C_{max} and AUC_{0-336h} at steady state in patients with statins as add-on therapy receiving a 75mg dose Q2W (n=34) were compared between Chinese and non-Chinese (i.e., from a previous analysis in non-Chinese patients compounded of 317 Caucasians/Blacks and 14 non-Chinese Asians [1])

Results

Informative priors on all model parameters (population PK, covariate, inter-individual variability and residual error parameters) were required for model stability and precision of parameter estimates.

Individual and population predictions were in good agreement with observations and did not reveal any trends with observed concentrations or time. The AFE, rmse% and mpe% were, respectively, 1.56, 60.7% and 9.58% for population and 1.17, 25.9% and 3.49% for individual predictions.

Parameter estimates in the Chinese population were close to those previously found in non-Chinese, with a maximal difference of -10 % on the variance of the Michaelis-Menten constant. Exposure parameters in Chinese patients were similar to those of non-Chinese patients (see Fig. 2).

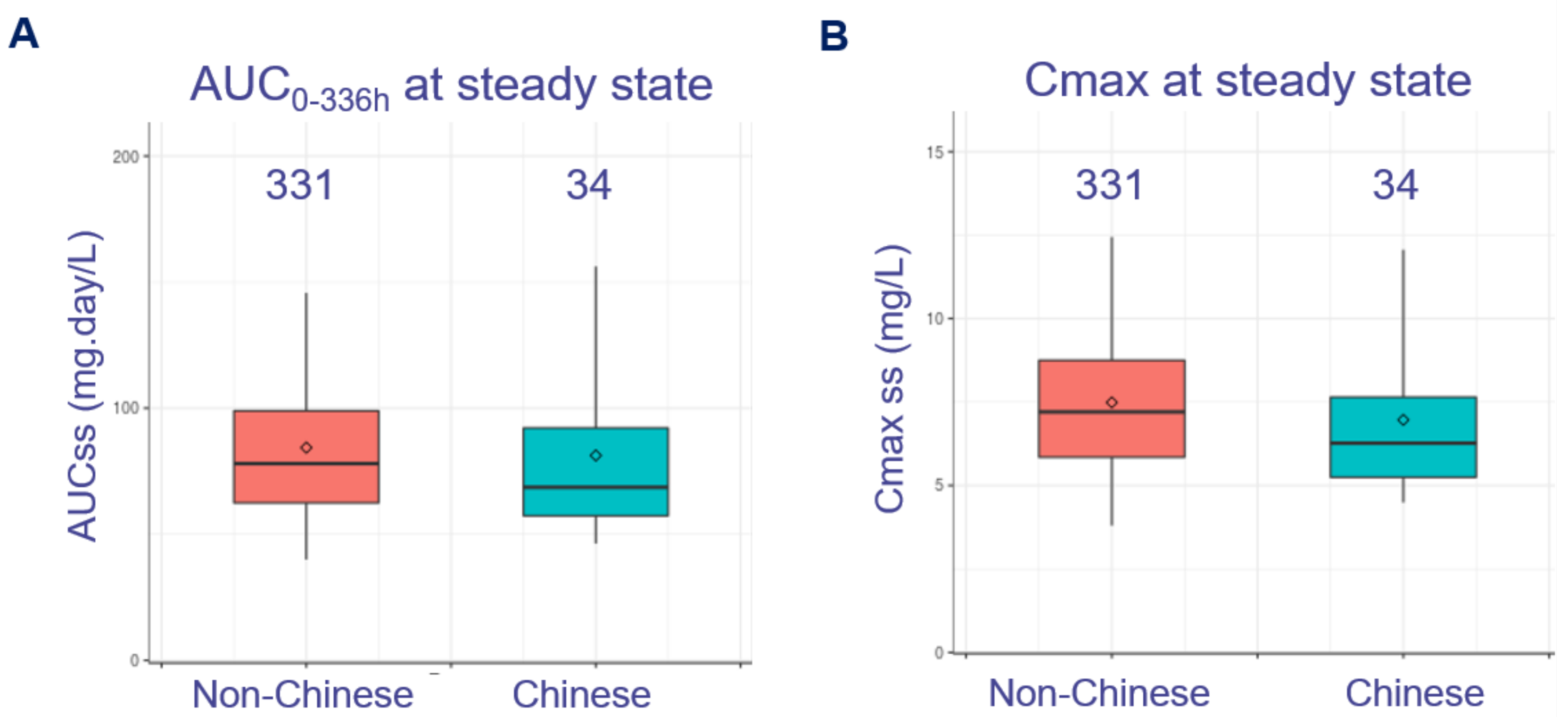


Fig. 2 Alirocumab steady state AUC_{0-336h} (A) and C_{max} (B) in Chinese (in green), and non-Chinese (Caucasian/Black/non-Chinese Asians in orange) patients following a 75 mg every two weeks regimen as add-on therapy to statins. The boxplots present the 5th, 25th, median, 75th and 95th percentiles. The diamond symbol represents the mean.

Conclusions and Perspectives

The use of the PRIOR approach allowed for the building and qualification of a POPPK model in a small dataset of Chinese patients, and ultimately for the estimation of individual C_{max} and AUC_{0-336h} at steady state. These exposure parameters were close to those reported in the non-Chinese population.

The individual parameters estimates will be later on used for the PKPD modelling of the relationship between alirocumab concentrations and LDL-C decrease in the Chinese population.

References:

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