

Modelling and simulation of alirocumab – Part 1: Population pharmacokinetic analysis using a Michaelis-Menten approximation of the target-mediated drug disposition model

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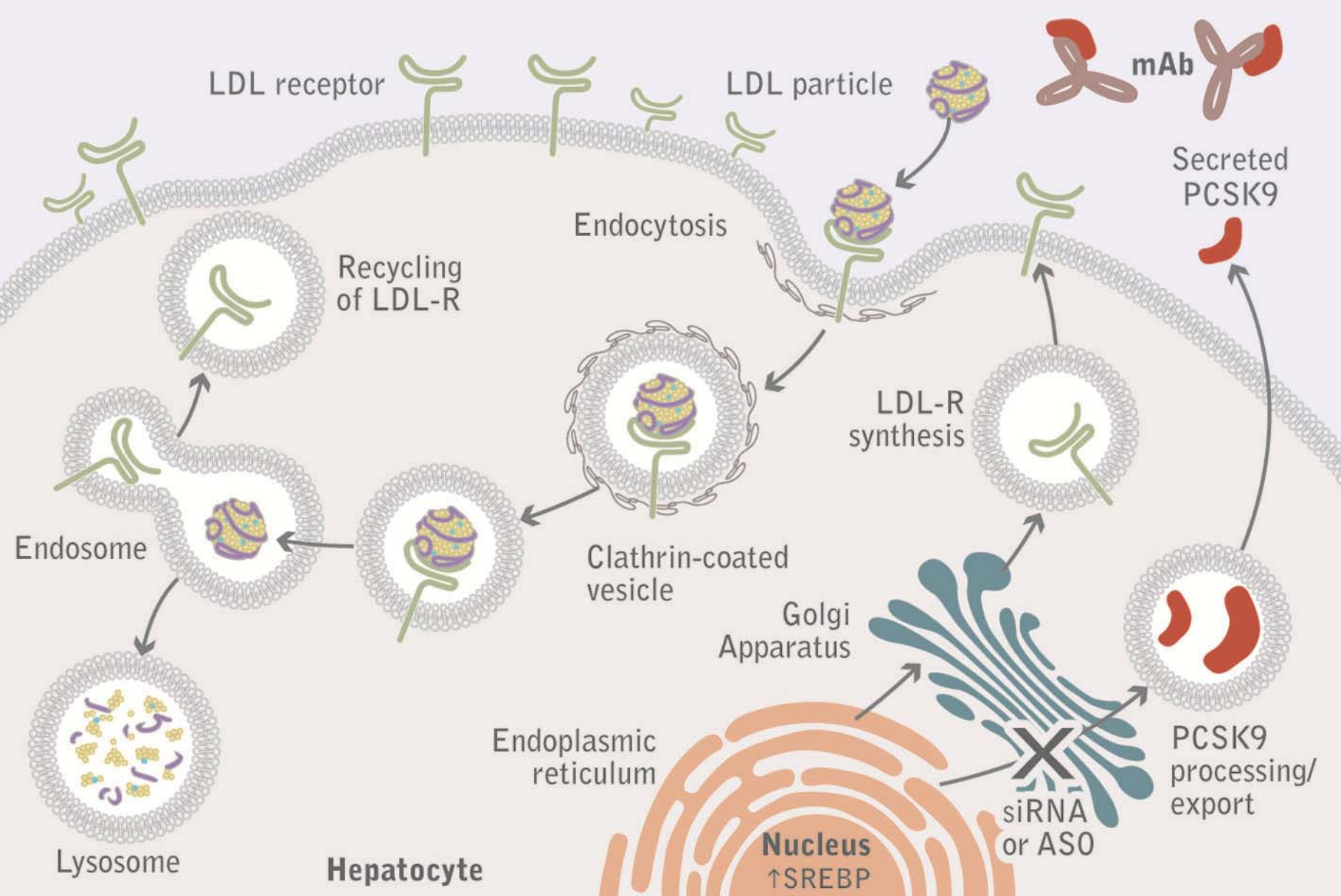
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Background

Alirocumab, a monoclonal antibody against PCSK9 approved in several countries, significantly reduces LDL-C levels both alone and when combined with other lipid-lowering therapies. Briefly, blocking PCSK9 activity represents a novel therapeutic modality that, although different from all currently available therapies, shares a part of the mechanism of action of statins by increasing the number of LDL receptors on the surface of hepatocytes.

The objectives of this analysis were to:

- Develop and qualify a PopPK model of alirocumab in pooled data from Phase 1, 2 and 3 clinical studies.
- Explore the potential impact of covariates (demographic covariates, concomitant medications of other lipid-lowering therapies, antibody drug status, disease status, administration site and device, relevant biologic constants and renal function) on the population parameters.
- Provide the individual PK parameters to be used for the subsequent population PK/PD study.
- Compute individual exposure parameters of alirocumab (such as C_{max} , t_{max} and AUC_{0-7}) in a sparse data situation.



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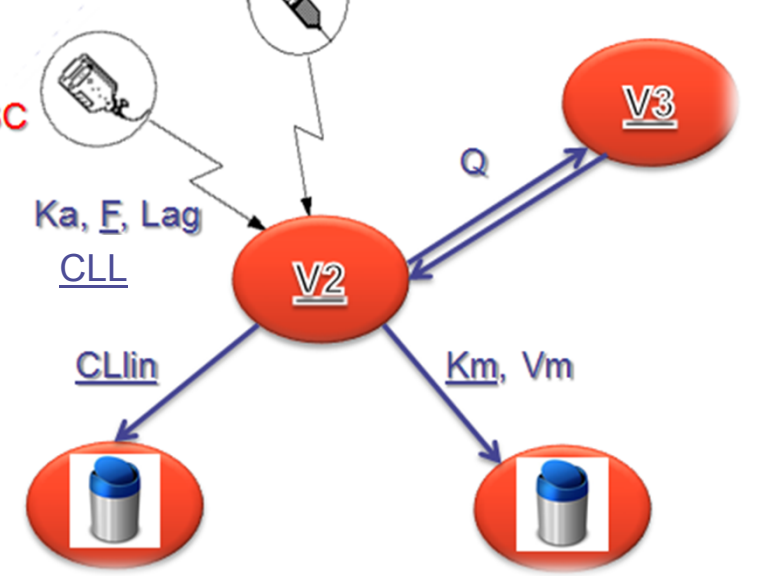
Methods

The dataset was composed of data from 13 clinical studies detailed in Table 1, performed in subjects with elevated LDL-C levels and patients suffering from hypercholesterolaemia (2799 patients and 13,717 alirocumab concentrations).

The PopPK analysis was performed with the NONMEM computer program (version 7.2) running on a LINUX cluster of multi-processor computers. All runs were performed using the First Order Conditional Estimate method with Interaction option.

Initially, outlier concentration-time points were detected and potentially excluded. Then the best pharmacostatistical model was selected; among the available approximations of the TMDD model, the Michaelis-Menten approximation was found to be a good compromise between model accuracy and computational time. In a second step, the relationship between the individual estimates and the covariates was investigated. Once developed, the model was validated using VPC and bootstrap methods. Lastly, individual PK parameters were used to compute patients' exposures.

Table 1. Summary of the clinical studies included in the analysis					
Study number	N	Input route	Alirocumab dose	Dosing regimen	PK samples
CL-0902	30	IV	0.3, 1, 3, 6, 12 mg/kg WT	Single dose	17
CL-0904	24	SC	50, 100, 150, 250 mg	Single dose	18
CL-1001	55	SC	50, 100, 150, 200 mg	Day 1, Day 29, Day 43 (E4W, E2W)	13
				Day 1, Day 29 (E4W)	
CL-1003	62	SC	150, 200, 300 mg	E4W (Weeks 0, 4, 8)	10
TDU12190	24	SC	100, 150, 250, 300 mg	Single dose	14
PKD12910	72	SC	150 mg	E2W (Weeks 0, 4, 8, 10)	12
DFI11565	149	SC	50, 100, 150 mg	E2W (Weeks 0, 2, 4, 6, 8, 10)	9
DFI11566	60	SC	200, 300 mg	E4W (Weeks 0, 4, 8)	8
DFI12361	75	SC	150 mg	E2W (Weeks 0, 2, 4, 6)	9
EFC11716	52	SC	75 mg (up to titration Week 12)	E2W (Week 0 to 24)	5
EFC11569	447	SC	75 mg (up to titration, Week 12)	E2W (Week 0 to 102)	5
EFC12492	309	SC	75 or 150 mg (up to Week 102)	E2W (Week 0 to 76)	5
LTS11717	1512	SC	75 or 150 mg (up to Week 76)	E2W (Week 0 to 76)	4



Results

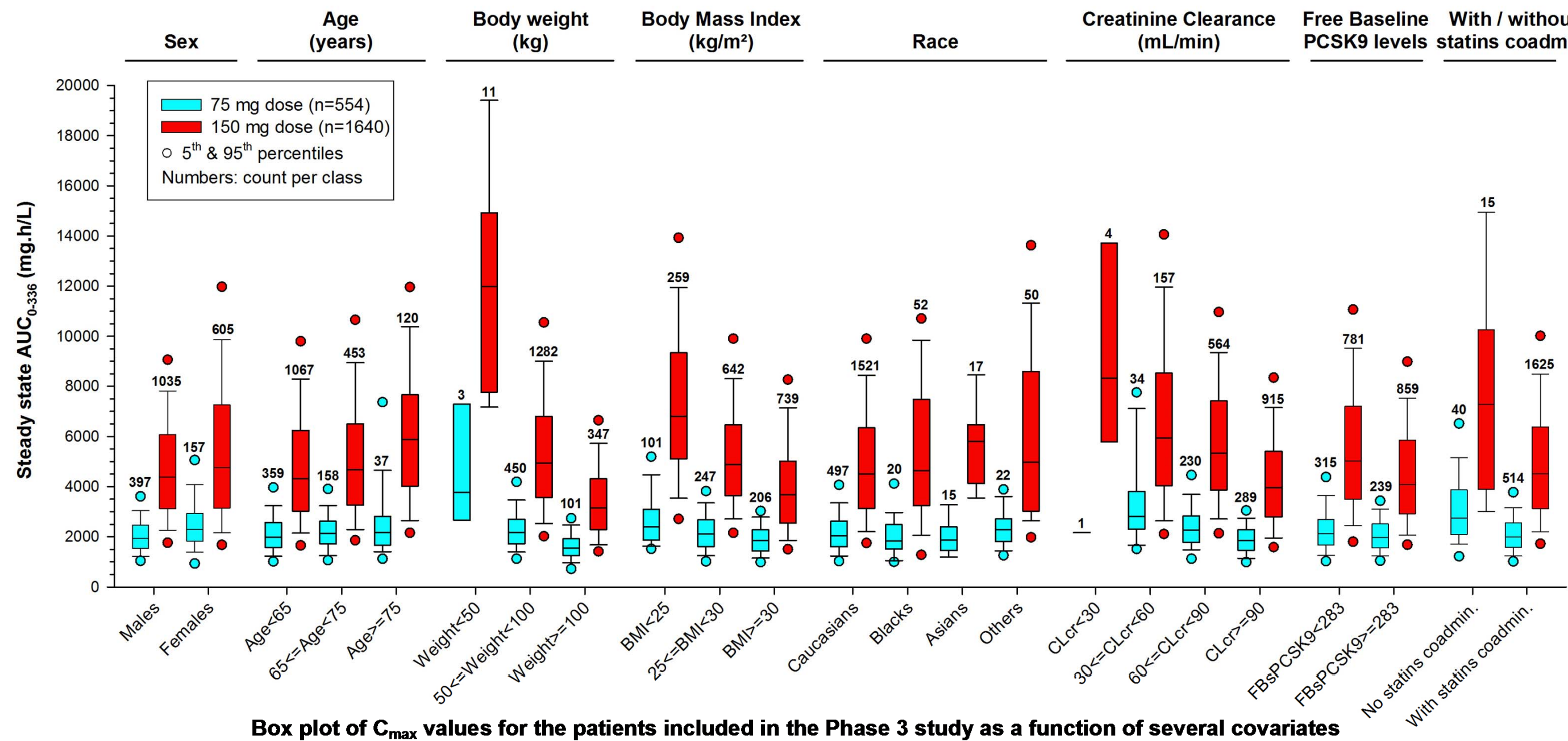
The model was a two-compartment model with a first order absorption process from the depot to the central compartment parameterised in terms of absorption constant (K_a , h^{-1}). Two elimination processes from the central compartment were used: a linear one, represented by a linear elimination clearance (CL_L , L/h) and a non-linear one, represented by the two Michaelis-Menten parameters V_m (mg/h) and K_m (mg/L). The two compartments were represented by a distribution volume (V_2 & V_3 for the central and the peripheral compartments, respectively) and linked by an inter-compartmental clearance Q . A lag-time and the bioavailability factor F (estimated using a logit function) completed the set of fixed effect model parameters θ s. The final PopPK model included two covariates on the linear elimination clearance CL_L , one on the Michaelis-Menten parameter K_m and one on the volume of distribution of the peripheral compartment V_3 .

CL_L was related to weight and to patient's coadministration of any statin according to the following equation:
 $CL_L = TVCL_L + COV_1 \times (WT - 82.9) + COV_2 \times STATIN$

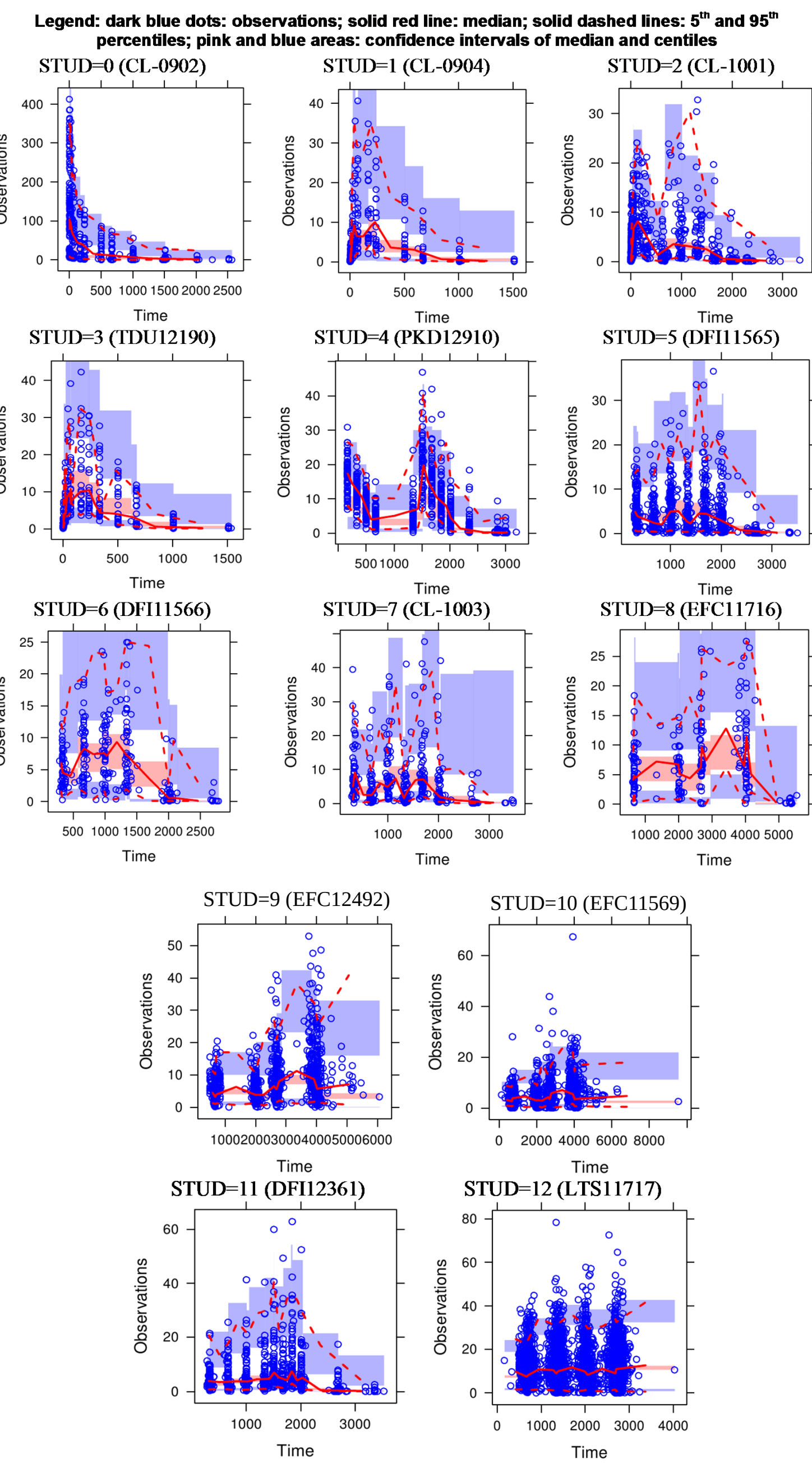
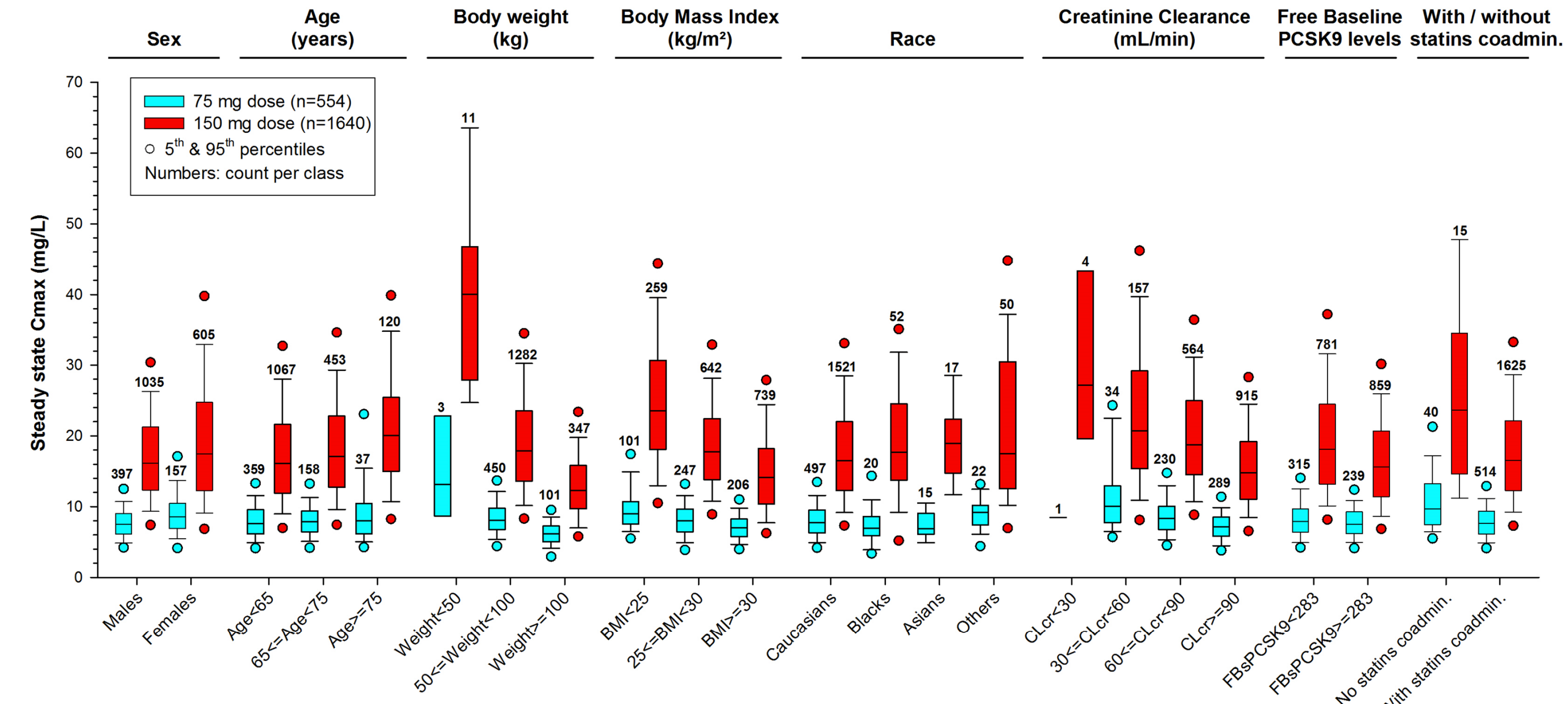
K_m was related to free time-varying PCSK9 serum levels (FPCSK) according to the following equation: $K_m = TVK_m + COV_3 \times \frac{FPCSK}{72.9}$

V_3 was related to age according to the following equation: $V_3 = TVV_3 \times \left(\frac{AGE}{60}\right)^{COV_4}$

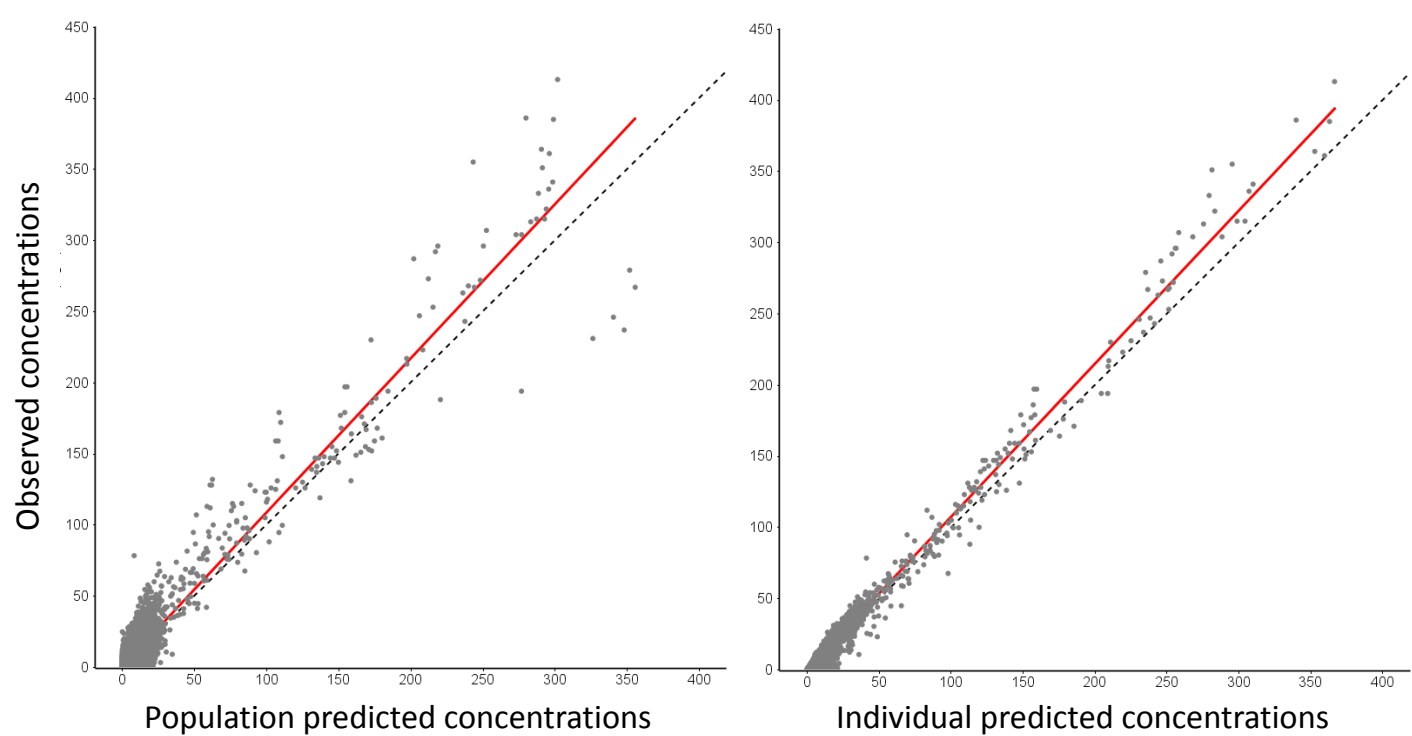
Individual exposures were obtained for all patients included in the analysis. Box plot of AUC values for the patients included in the Phase 3 study as a function of several covariates



Box plot of C_{max} values for the patients included in the Phase 3 study as a function of several covariates



All the acceptance criteria were reached and both the graphical and the numerical quality criteria show the quality of the fit.



Conclusions

This model was part of the alirocumab biologics license application and allowed prediction of the alirocumab PK properties as well as individual exposures. It also allowed the identification of covariates that explained a part of the inter-individual variability of the compound. Thus, CL_L was related to body weight and co-administration of any statin, K_m was related to free time-varying PCSK9 serum levels, and V_3 was related to age. The impact of the inclusion of age on V_3 was very limited: 2.99 L for a 75-year-old patient and 2.86 L for a 65-year-old patient in comparison with 2.79 L for a 60-year-old patient. The impact of time-varying free anti-PCSK9 concentration on the Michaelis-Menten parameter K_m was significant. When considering the 5th (<31 ng/mL, LOQ) and 95th (392 ng/mL) percentiles of time-varying free PCSK9 levels in the study population, K_m was 7.73 ng/mL and 4.82 ng/mL, respectively. The most important effect was observed on CL_L , which was decreased by 78% in patients weighing 50 kg and increased by 40% in patients weighing 100 kg, in comparison with a typical patient weighing 82.9 kg (~median weight). In a typical patient weighing 82.9 kg, CL_L was increased by 52% when co-administered with a statin. Despite the quite important impact of covariates, especially on CL_L , the impact of covariates on alirocumab exposure did not translate into any clinically meaningful difference in efficacy or safety profile, in part because up-titration of dose accommodated any potential effects.

Acknowledgements

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Disclosures

Martinez JM, Brunet A, Hurbin F, Rauch C and Fabre D are employees of Sanofi. DiCioccio TA is an employee of Regeneron. Lohan L is a pharmacy resident from the Montpellier's Faculty of Pharmacy. The opinions, conclusions and interpretation of the data are the responsibility of the authors.

Glossary

%RSE, percentage of relative standard error (100% * SE/estimate); AUC_{0-T} , area under the concentration-time curve; BMI, body mass index; CLcr, creatinine clearance; CL_L , linear clearance; C_{max} , maximum concentration; EZE, ezetimibe; F, bioavailability; FPCSK9, free PCSK9 concentration; FBPCSK9, free baseline PCSK9 concentration; FDA, American Food and Drug Administration; IV, intravenous; K_a , 1st-order absorption rate constant; K_m and K_m , Michaelis-Menten parameters; Lag, lagtime; LDL-C, low-density lipoprotein cholesterol; LOQ, limit of quantitation; PCSK9, proprotein convertase subtilisin/kexin type 9; PD, pharmacodynamics; PK, pharmacokinetic; PopPK, population pharmacokinetics; Q, intercompartmental clearance; SC, subcutaneous; t_{max} , time taken to reach maximum concentration; TMDD, target mediated drug disposition model; VPC, visual predictive check; V, volume; VPC, visual predictive check.