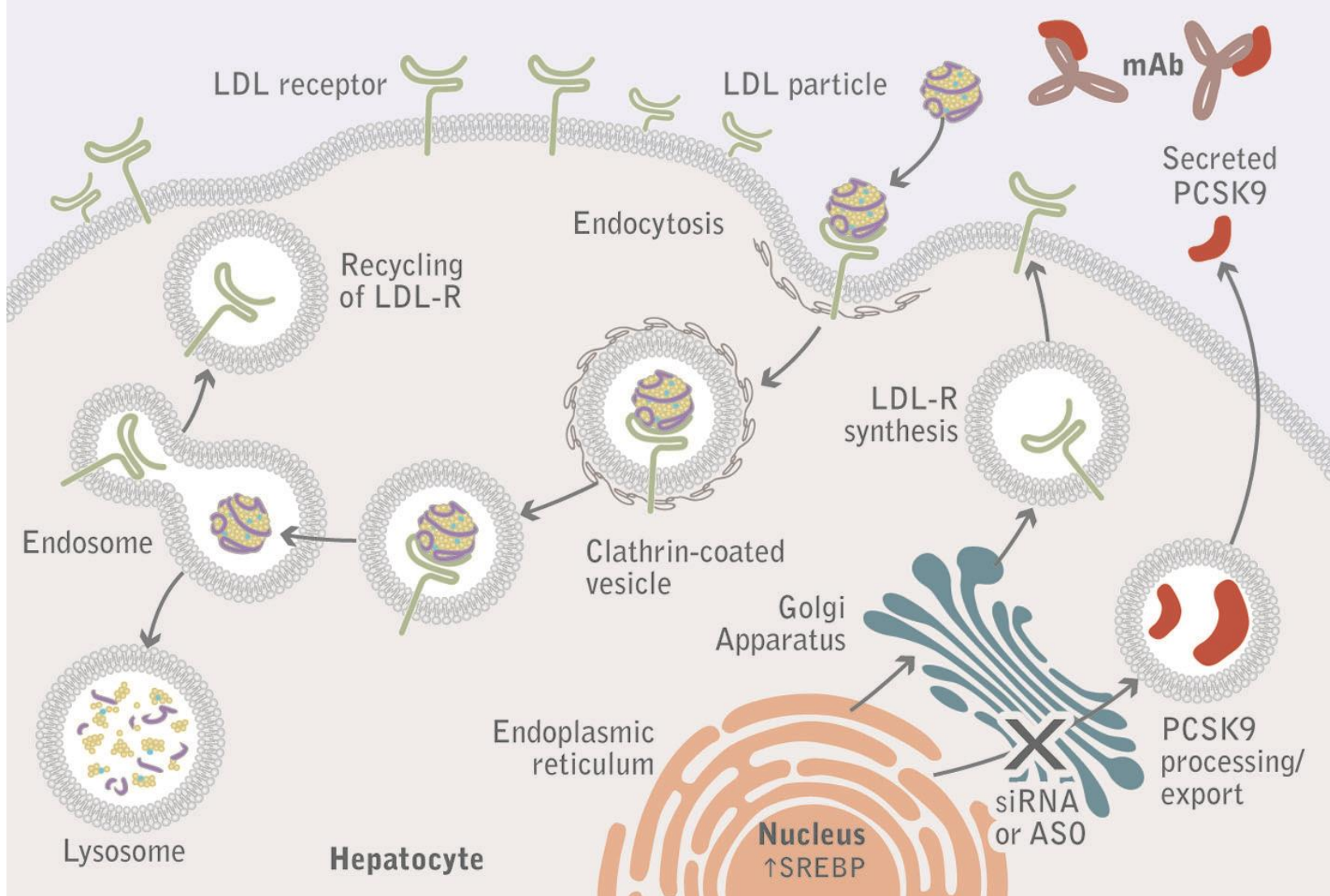


Modelling and simulation of alirocumab – Part 2: Population pharmacokinetic/ pharmacodynamic analysis using an indirect response model to link alirocumab concentrations with LDL-C

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Background

Alirocumab, a monoclonal antibody against PCSK9 approved in several countries, significantly reduces low-density LDL-C levels both alone and when combined with other LLTs. 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.



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The main objective of this analysis was to develop and qualify a PopPK/PD model, analysing the relationship between alirocumab concentrations and LDL-C in a pool of data from clinical studies (Phase 1, 2, and 3). Another objective was to explore the potential relationships between population PD parameter and demographic covariates, relevant co-administration, type of disease, and relevant biologic constants.

Lastly, the individual derived PD parameters (Δ LDL-C_{max} and Δ LDL-C_{trough}) were to be estimated for the first and the last administrations for a pool of Phase 1/2 studies and for the intervals between Weeks 10–12 or between Weeks 22–24 for Phase 3 studies.

Methods

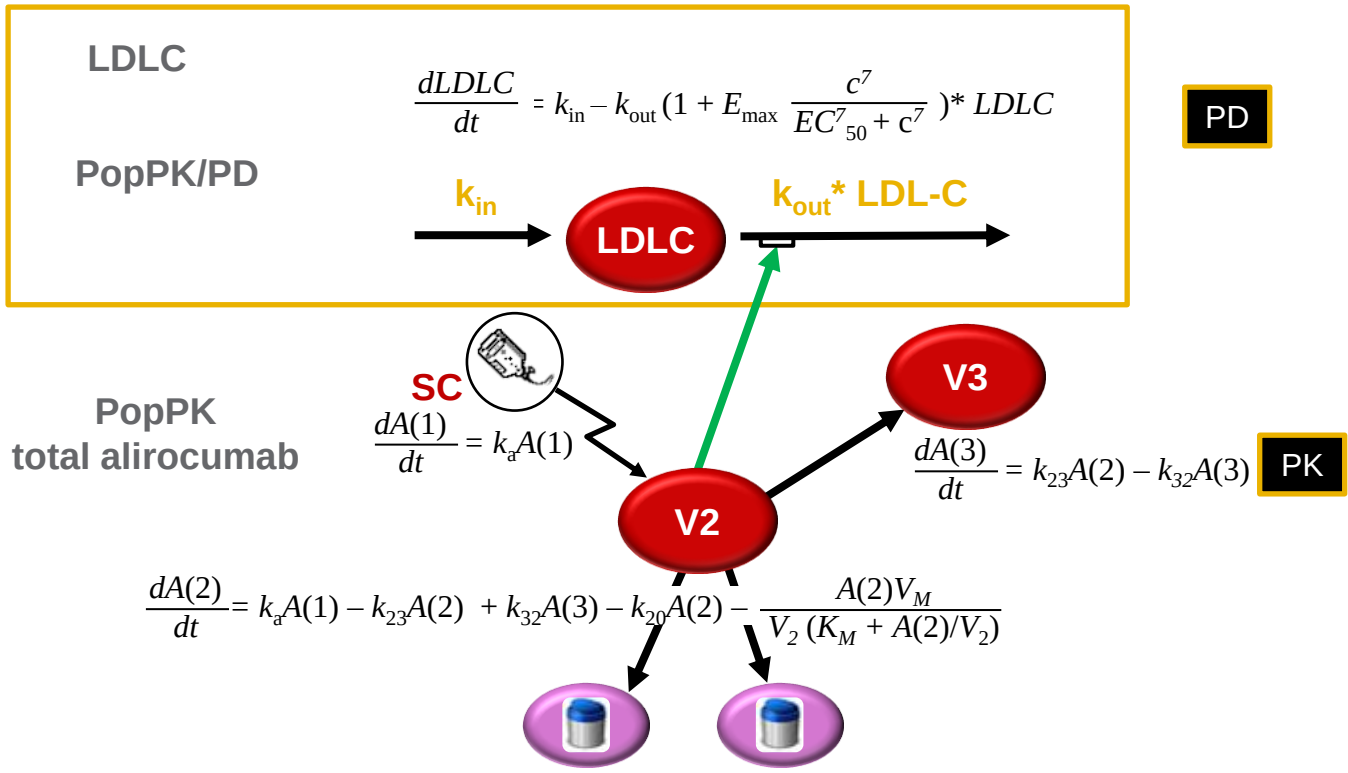
Data description

The dataset was composed of data from 13 clinical studies detailed in Table I, performed in subjects with elevated LDL-C levels and patients suffering from hypercholesterolaemia (2799 patients and 14346 LDL-C values).

The PopPK/PD model development was performed using a two-step procedure. In the first step, individual PK parameters from the PopPK model were used to calculate the alirocumab concentrations for all time points needed for the development of the PopPK/PD model. In the second step, the PopPK/PD relationship was analysed. Based on an exploratory PopPK/PD analysis, an indirect response model with Hill coefficient was used to link the alirocumab concentrations with LDL-C, via the stimulation of loss of response, Kout.¹

The model was developed with NONMEM 7.2 using the First Order Conditional Estimation method interaction.

Summary of clinical studies included in the analysis				
Study number	N	Input route	SAR236553 (alirocumab) dose	Mean PD samples per patient
CL-0902	30	IV	0.3, 1, 3, 6, 12 mg/kg WT	11
CL-0904	24	SC	50, 100, 150, 250 mg	9
CL-1001	54	SC	50, 100, 150 mg	12
CL-1003	61	SC	150, 200, 300 mg	8
TDU12190	24	SC	100, 150, 250, 300 mg	11
PKD12910	72	SC	150 mg	11
DFI11565	149	SC	50, 100, 150 mg	7
DFI11566	60	SC	150 mg	6
DFI12361	75	SC	50, 75, 150 mg	10
EFC11716	52	SC	75 mg (until Week 12) 75 or 150 mg (until Week 24)	5
EFC11569	434	SC	75 mg (until Week 12) 75 or 150 mg (until Week 102)	5
EFC12492	296	SC	75 mg (until Week 12) 75 or 150 mg (until Week 76)	5
LTS11717	1460	SC	150 mg (until Week 76)	4



Results

During the pharmacostatistical model development, the inter-individual variability was evaluated for each model parameter and then estimated for all the PD model parameters. The combined (additional and proportional) residual error model was selected. The influence of the estimation of covariance between η s within an ω -block was assessed; none of them were retained since there was no improvement of the model quality. The following available standard demographic variables (sex, age, disease status, WT, BMI), albumin, mono-therapy vs co-medications such as statin or ezetimibe, baseline LDL-C, and free (FBSPCSK9) or total PCSK9 (TBSPCSK9) at baseline or longitudinal were screened (univariate model) in order to assess their impact upon Kout, EC₅₀, E_{max}, and γ . The available potential sources of variability on the population PD parameters were extensively investigated. As detailed in the table below, 10 covariates were included in the model, either on E_{max} (time-varying total PCSK9, sex, age, WT, FBSPCSK9, and co-administration of statins), EC₅₀ (TBSPCSK9 and co-administration of high impact statins), Kout (DISST, healthy volunteers or patients), or on the Hill coefficient γ (FBSPCSK9).

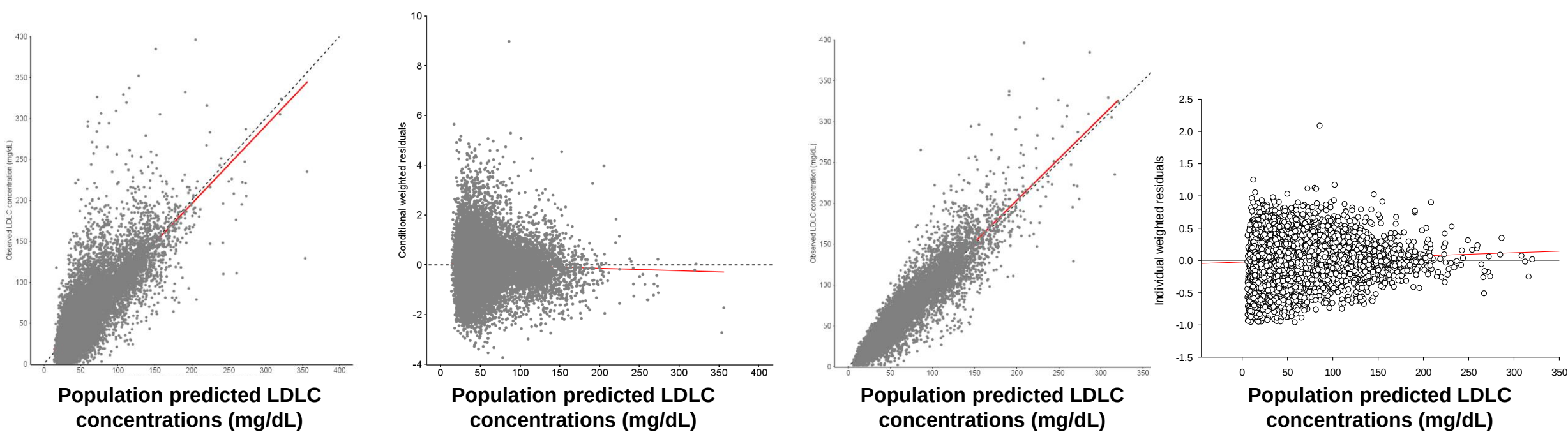
Pharmacostatistical model		Final model with covariates		[95% CI]
Parameter	Estimate	% RSE	Estimate	
Typical value of Kout (h ⁻¹)	0.00522	4.77%	0.00395	6.74 [0.00342; 0.00449]
Effect of DISST on Kout (h ⁻¹)	NA	NA	0.00997	5.73 [0.00883; 0.0111]
Typical value of EC ₅₀ (h ₂ , mg/L)	3.95	2.74 %	1.44	13.0 [1.07; 1.82]
Effect of TBSPCSK9 on EC ₅₀ (h ₂)	NA	NA	0.00219	12.4 [0.00164; 0.00273]
Effect of HDSTATIN on EC ₅₀ (h ₂)	NA	NA	1.21	3.89 [1.11; 1.30]
Typical value of E _{max} (h ₂)	2.72	2.07%	2.43	4.07 [1.63; 1.92]
Effect of TPCSK9 on E _{max} (h ₂)	NA	NA	0.000331	3.69 [0.000306; 0.000355]
Effect of SEX on E _{max} (h ₂)	NA	NA	0.703	3.71 [0.651; 0.755]
Effect of AGE on E _{max} (h ₂)	NA	NA	0.415	15.6 [0.286; 0.545]
Effect of WT on E _{max} (h ₂)	NA	NA	0.313	26.7 [0.146; 0.480]
Effect of FBSPCSK9 on E _{max} (h ₂)	NA	NA	0.00156	19.1 [0.000965; 0.00215]
Effect of STATIN on E _{max} (h ₂)	NA	NA	0.408	20.4 [0.242; 0.575]
Typical value of γ (h ₂)	2.18	4.33%	1.78	4.07 [1.63; 1.92]
Effect of FBSPCSK9 on γ (h ₂)	NA	NA	0.00340	13.3 [0.00249; 0.00430]
Inter-individual variability (CV%)				
Parameter	Estimate	% RSE	Estimate (CV%)	% RSE [95% CI] (Shrinkage %)
ω Kout	0.633 (79.6%)	7.92%	0.113 (33.7%)	33.7% [0.30369; 0.190] (82.4%)
ω EC ₅₀	0.089 (29.9%)	12.5%	0.123 (35.1%)	12.6% [0.0921; 0.154] (64.5%)
ω E _{max}	0.491 (70.1%)	3.13%	0.420 (65.8%)	3.01% [0.395; 0.445] (11.2%)
ω γ	0.422 (65.0%)	11.8%	0.296 (54.4%)	12.5% [0.222; 0.371] (61.3%)
Residual variability				
Additive term (η , mg/dL)	5.148	2.13%	5.21	2.13% [4.99; 5.43]
Proportional term (η)	0.223	0.57%	0.224	0.59% [0.221; 0.227]

Once the PopPK/PD model had been developed and validated, the model parameters were used to derive individual exposures (Δ LDL-C_{max} and Δ LDL-C_{trough} in the dosing interval) for subcutaneous Phase 1, 2 and 3 patients (n=2799).

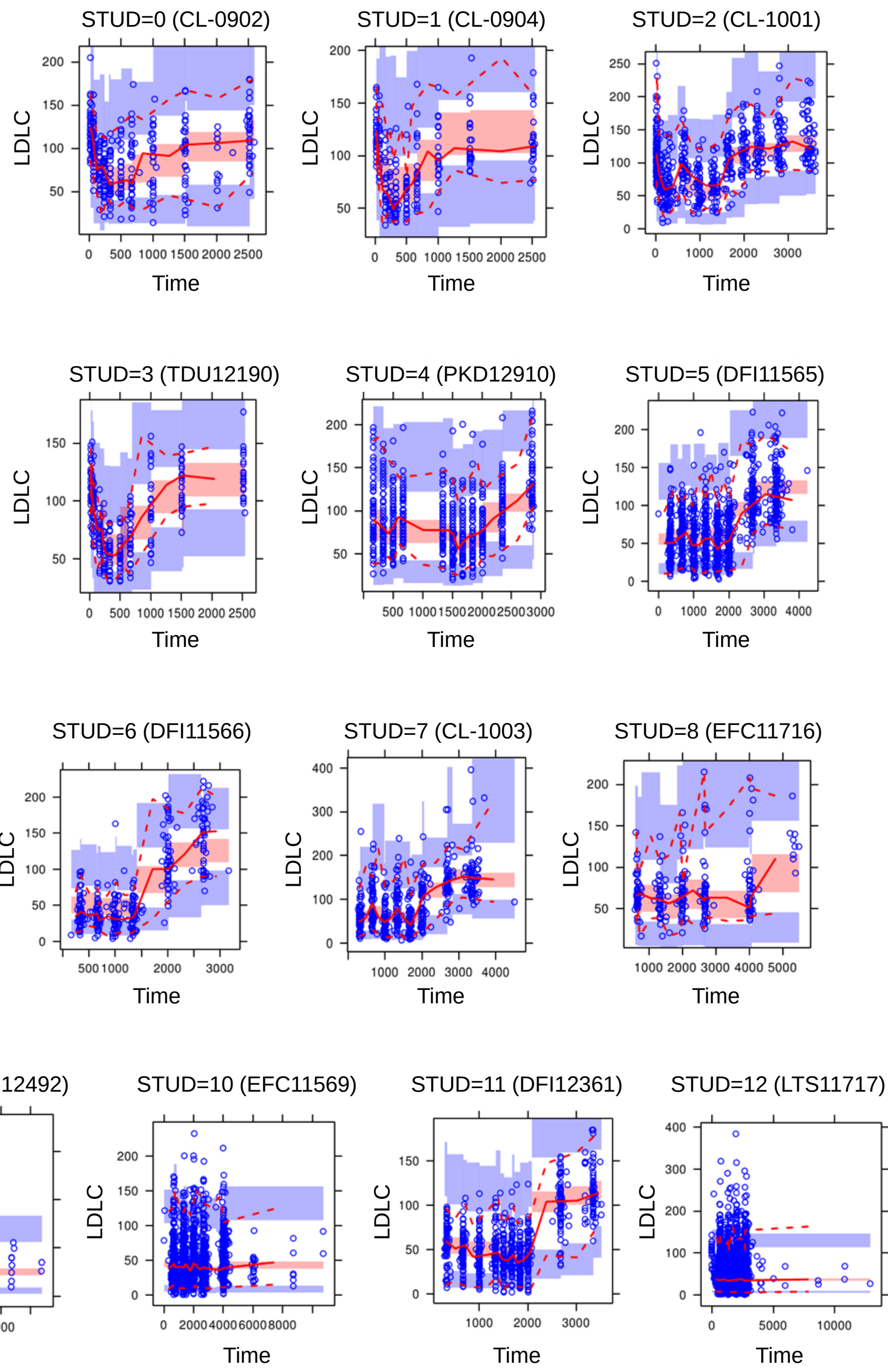
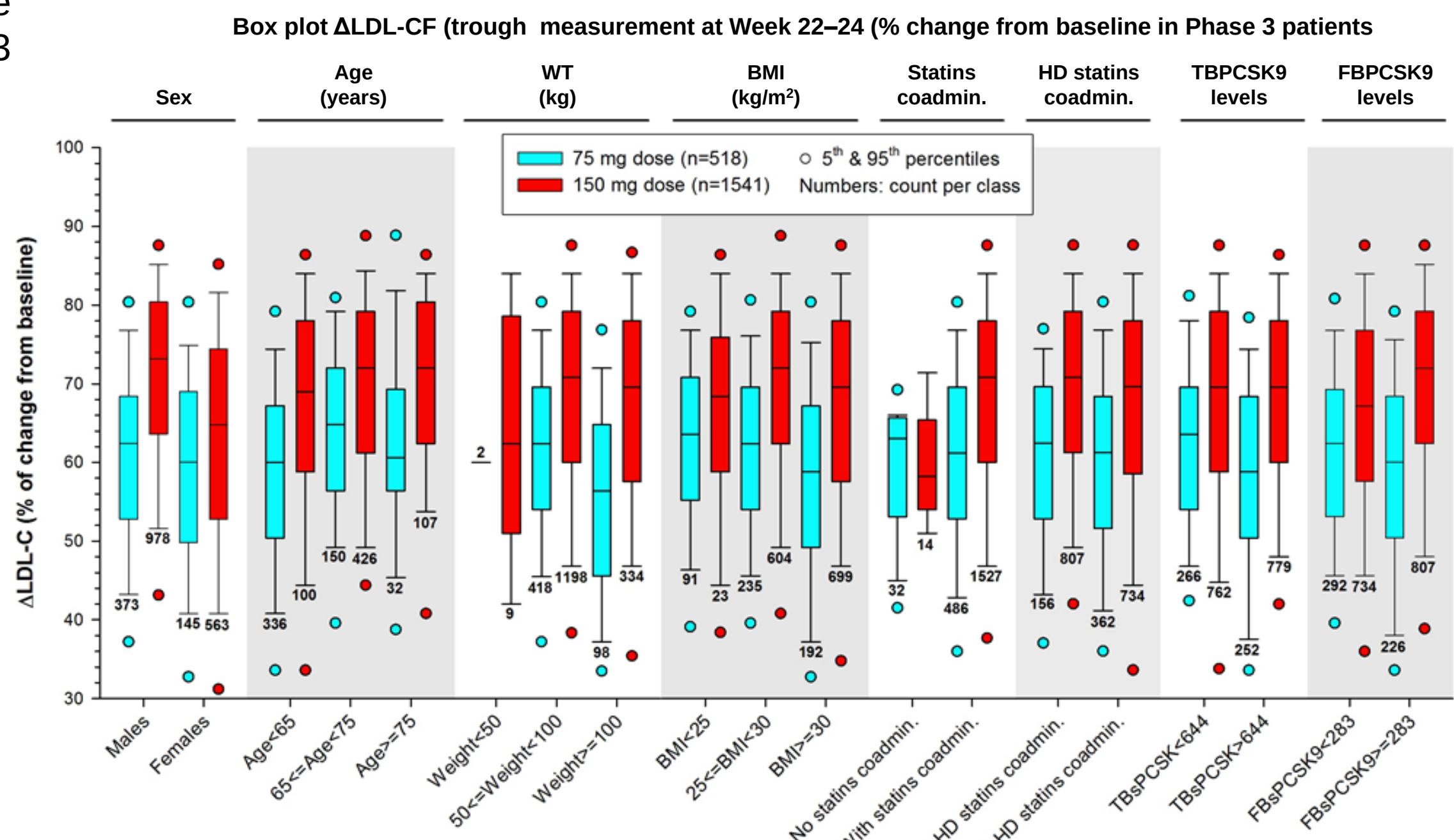
Descriptive statistics of PD parameters for the patients included in the Phase 3 studies (i.e. EFC11569 – EFC11716 – EFC12492 – LTS11717) at Week 10–12									
Δ LDL-C _{max} (%)									
Dose	N	Mean	CV	STD	Min	P5	Median	P95	Max
75	754	62.1	23.9	14.8	0	32.4	63.6	82.8	92.4
150	1407	71.5	18.7	13.4	16.8	45.6	74.4	88.8	94.8
Δ LDL-C _{trough} (%)									
75	754	54.6	29.2	15.9	0	24.0	56.4	78.0	92.4
150	1407	68.9	21.0	14.5	8.40	40.8	70.8	87.6	93.6
Descriptive statistics of derived PD parameters for the patients included in the Phase 3 studies (i.e. EFC11569 – EFC11716 – EFC12492 – LTS11717) at Week 22–24									
Δ LDL-C _{max} (%)									
Dose	N	Mean	CV	STD	Min	P5	Median	P95	Max
75	518	67.6	16.7	11.3	15.6	49.2	68.4	85.2	92.4
150	1541	70.4	20.1	14.1	6.00	43.2	73.2	88.8	93.6
Δ LDL-C _{trough} (%)									
75	518	60.2	21.6	13.0	7.20	36.0	61.2	80.4	91.2
150	1541	67.4	22.5	15.2	4.80	38.4	69.6	87.6	93.6

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

For the 13 studies included in this analysis, the results of the visual predictive check showed that a large majority of the observed LDL-C were included in the range [5th–95th percentiles] and represent a good qualification of the PopPK/PD model.



Quality criteria	PRED vs OBS (mg/dL)	IPRE vs OBS (mg/dL)
Bias [95% CI] (% mean OBS)	2.44 [2.02; 2.87] (4.04%)	0.919 [0.670; 1.17] (1.51%)
Precision [95% CI] (% mean OBS)	25.9 [25.1; 26.8] (42.8%)	15.3 [14.8; 15.7] (25.2%)
Correlation (r); Slope; Intercept	0.783; 0.644; 19.1	0.930; 0.850; 8.17
Average fold error	1.44	1.21



Conclusions

The indirect population pharmacodynamic response model, describing the relationship between alirocumab concentrations and LDL-C levels, was developed and validated with data from 13 clinical studies. Ten covariates were included into the model to explain the between-patient variability. The impact of the covariates on E_{max} was moderate to important; depending on the covariate there was about a 25% increase for time-varying PCSK9, age, body weight, and FBSPCSK9, with an increase of 29.7% for males compared with females and only 16.8% in the presence of a statin. The impact on TBSPCSK and high impact statins on EC₅₀ was moderate to important: a 1.77-fold increase of EC₅₀ was observed for total PCSK9 but only a 20.6% increase when co-administered with a high level of statins. The impact of baseline FBSPCSK9 on the Hill coefficient γ was important: a two-fold increase of γ was observed. The impact of DISST on Kout value was important: a 2.52-fold increase was observed in patients compared with healthy volunteers. However none of those covariate had a clinically significant impact on LDL-C reduction with a 75 mg/150 mg Q2W dosing regimen.

Finally, this model allowed the characterisation of the PopPK/PD properties of alirocumab in its target population and the estimation for each patient of LDL-C concentrations and derived parameters (Δ LDL-C_{max} and Δ LDL-C_{trough}).

References

1. Jusko WJ, Ko HC. *Clin Pharmacol Ther.* 1994;56:406–419.

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Disclosures

All authors are employees of Sanofi. The opinions, conclusions, and interpretation of the data are the responsibility of the authors.

Glossary

% RSE, % of relative standard error; BMI, body mass index; CI, confidence interval; C_{max}, maximum concentration; C_{trough}, trough concentration; CV%, coefficient of variation percentage; DISST, binary variable coding for healthy volunteers versus patients; E2W, every 2 weeks; E4W, every 4 weeks; EC₅₀, concentration to reach 50% of the maximum effect; E_{max}, maximum effect; FBSPCSK, free baseline PCSK9 concentration; FDA, American Food and Drug Administration; HC, hypercholesterolemia; HD statin, high dose statin; HV, healthy volunteers; IPRE versus OBS; individual predictions versus observed; IV, intravenous; Kout, first-order rate constant for loss of response; LDL-C, low-density lipoprotein cholesterol; LDL-R; low-density lipoprotein receptor; LLTs, lipid-lowering therapies; mAb, monoclonal antibody; N, numbers of patients/subjects; NA, not applicable; PCSK9, proprotein convertase subtilisin/kexin 9; PD, pharmacodynamic; PK, pharmacokinetic; PopPK/PD, population pharmacokinetic/pharmacodynamics; PRED vs OBS; population predictions vs observed; SC, subcutaneous; siRNA, small interfering RNA; TBSPCSK9, total baseline PCSK9 concentration; γ , the modelled value for the dependent variable under the statistical model; WT, weight.