

Population PK with full and reduced covariate models for Sym004, an antibody mixture targeting EGFR

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Background and Objectives

Sym004 is a mixture of two monoclonal antibodies (futuximab & modotuximab) that bind to two non-overlapping epitopes on the epidermal growth factor receptor (EGFR) and synergistically inhibit the growth of cancer cells. Sym004 is a 2nd generation anti-EGFR therapy in late clinical development for treatment of solid tumors.

Using clinical PK and covariate data for Sym004, the objectives of this work were to:

- Update the preliminary population (Pop) pharmacokinetic (PK) model for Sym004 [1] to describe the available PK data from four clinical studies
- Build **full** and **reduced covariate models** and investigate how the method for calculating standard errors (SE) in the full covariate model impacts the interpretation of the covariate relationships and the selection of statistically significant covariates

A **full covariate model (FCM)** [2,3] comprises a base population PK model and inclusion of all candidate covariate relationships in one step.

In the **FCM**, the effect size and 95% confidence intervals (CI) for all candidate covariates provide interpretation of their clinical relevance: useful for regulatory purposes and labeling.

The **reduced covariate model (RCM)** is derived from the FCM and comprises only those covariates which are statistically significant for clinical relevance.

Data

Clinical Sym004 PK and covariate data from 330 patients participating in four Sym004 Phase 1 and 2 trials were pooled for the population PK analysis. Most patients had metastatic colorectal cancer (mCRC) (n=247) while the rest had various advanced solid tumors.

A wide dose range of 0.4 to 18 mg/kg was explored. Sym004 was dosed by i.v. infusion every week or every 2nd week, or as a 9 mg/kg loading dose followed by 6 mg/kg weekly (9/6 mg/kg weekly). A mix of full PK profiles and sparsely sampled PK provided 5341 data points.

The patient characteristics predefined as candidate covariates included demographics, markers for liver and kidney function, tumor types and size, patient performance and prior therapies.

Methods

Software

Modeling was done in NONMEM v7.3 (FOCEI).

Base model

- Due to non-linear PK: 2-compartment model with target mediated drug disposition (TMDD) using the Michaelis-Menten (MM) implementation (**Figure 1**).
- Weight included a priori.
- Proportional + additive error model.
- IIV on CL, V1, V2 and Vmax; full covariance matrix.

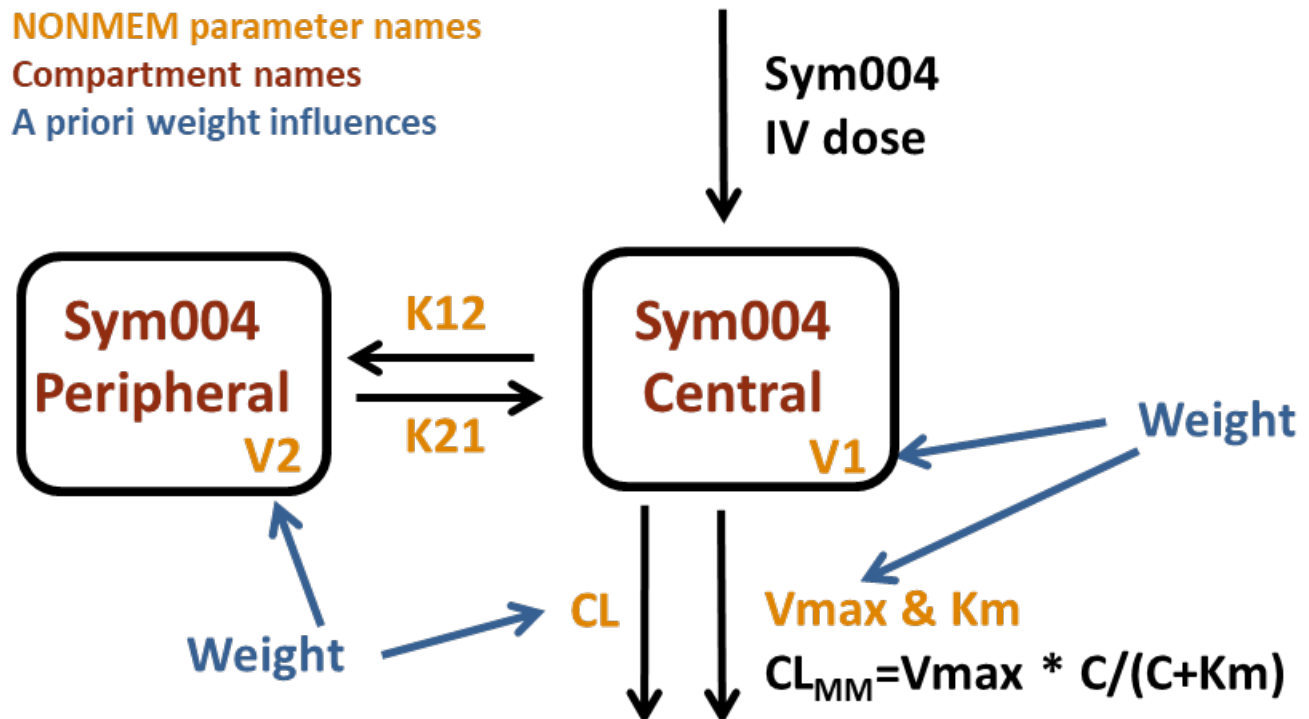


Figure 1. Structure of the base Sym004 PK model
CL: linear clearance, V1: central cmt, V2: peripheral cmt, K12 and K21: rate constants for distribution between V1 and V2, CL_{MM}: non-linear CL defined by Michaelis-Menten equation, C = Sym004 concentration.

Covariate model development

Workflow for full and reduced covariate models is outlined in **Figure 2**.

Four different methods for SE calculation of the estimates in the covariate models were compared:

- MATRIX RSR**: The default sandwich estimator in NONMEM (the variance-covariance matrix, MATRIX=RSR).
- MATRIX S**: the cross-product matrix, S, defined by the sum of the cross products of the gradient vectors of the $-2\ln(\text{individual} - \text{likelihood})$ (MATRIX=S in NONMEM).
- SIR**: The sampling importance re-sampling method (SIR) [4].
- Bootstrap**: 500 data sets sampled with replacement.

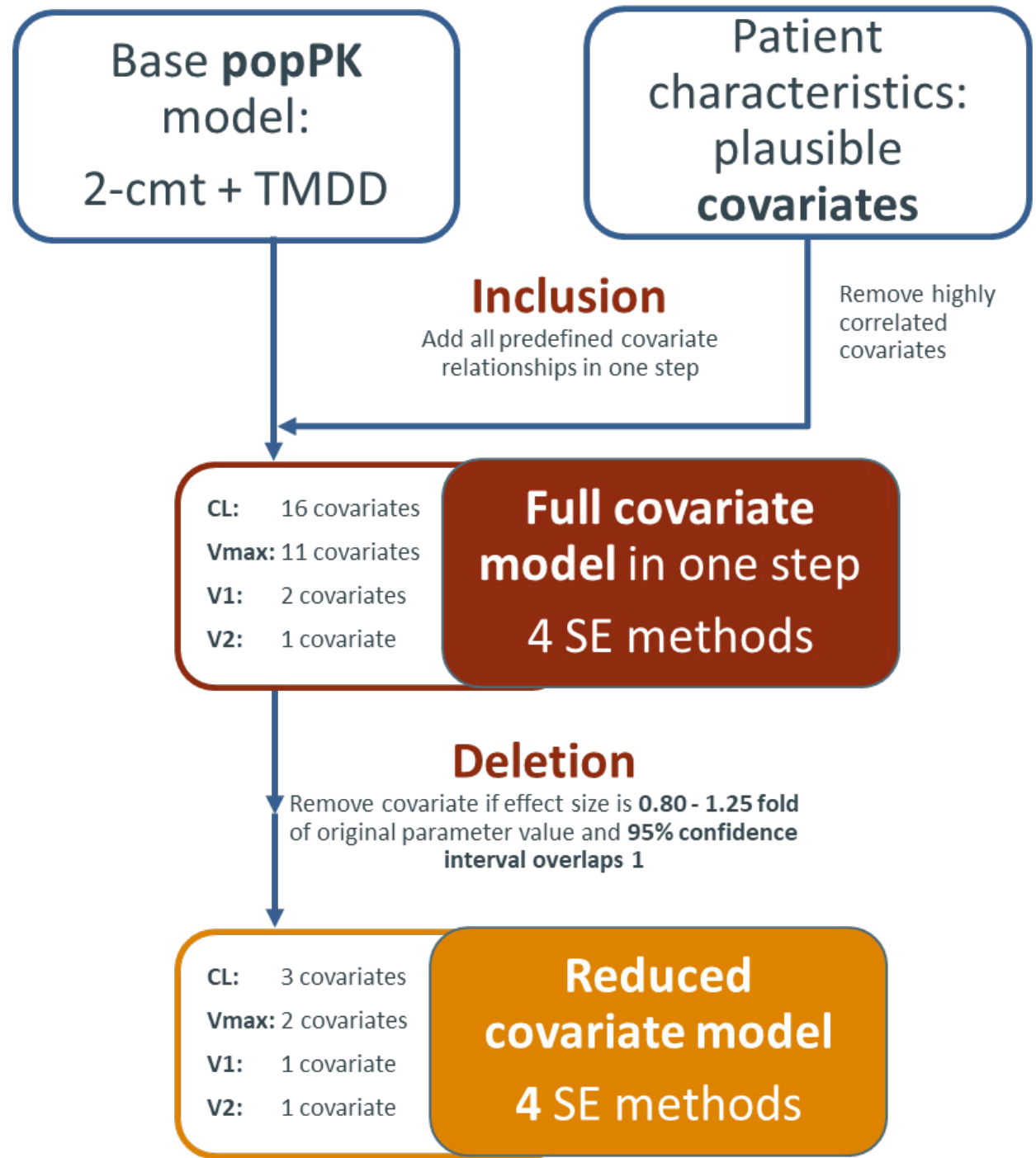


Figure 2. Covariate model development

The covariate effects for continuous covariates were scaled in the NONMEM control streams in such a way that the effect was quantified as a fold-change across 95% of the covariate range, e.g. for the effect of weight on CL:

$$CL = e^{\log(\Theta_1) + \eta_1 + \Theta_2 * \log\left(\frac{WT}{median(WT)}\right) / (\log(97.5^{th} \text{ quantile}(WT)) - \log(2.5^{th} \text{ quantile}(WT)))}$$

Taking the exponent of the Θ_2 estimate and its 95% confidence interval, resulted in the estimated fold-change in CL due to WT across 95% of the WT covariate range. Categorical covariates were similarly estimated as shift on the log scale and back-transformed to a fold-change.

Results

The base model provided a good fit to the data (VPC in **Figure 3**). The residual proportional error was low: 17.6%, and the parameters were estimated with good precision.

The one-step FCM with 30 covariates was successfully run in NONMEM, provided a good fit, but was slightly over-parameterized (condition number 1017).

The Forest plot for the FCM (**Figure 4**) shows which covariates might warrant dose modifications (effect size outside 0.8-1.25 fold), which have no clinical relevance (effect size within 0.8-1.25 fold), and for which more information may be needed (CIs wide or overlapping limits) [3].

Results

For most covariates in the FCM, the SE (CI) calculated by the four methods were comparable;

- The SEs from the bootstrap were slightly higher than for the sandwich method,
- SIR SE estimates that are reported to have strong theoretical advantages [4] provided the lowest SEs.

For covariates, which were poorly estimated (e.g. tumor type, Asian race), the MATRIX=S option provided overly-inflated estimates for the SEs.

The reduced covariate model (**Figure 5, Table 1**) provided well estimated parameters (condition number 53) and enabled simulations with potentially clinically relevant covariates (weight, albumin, sex, tumor size).

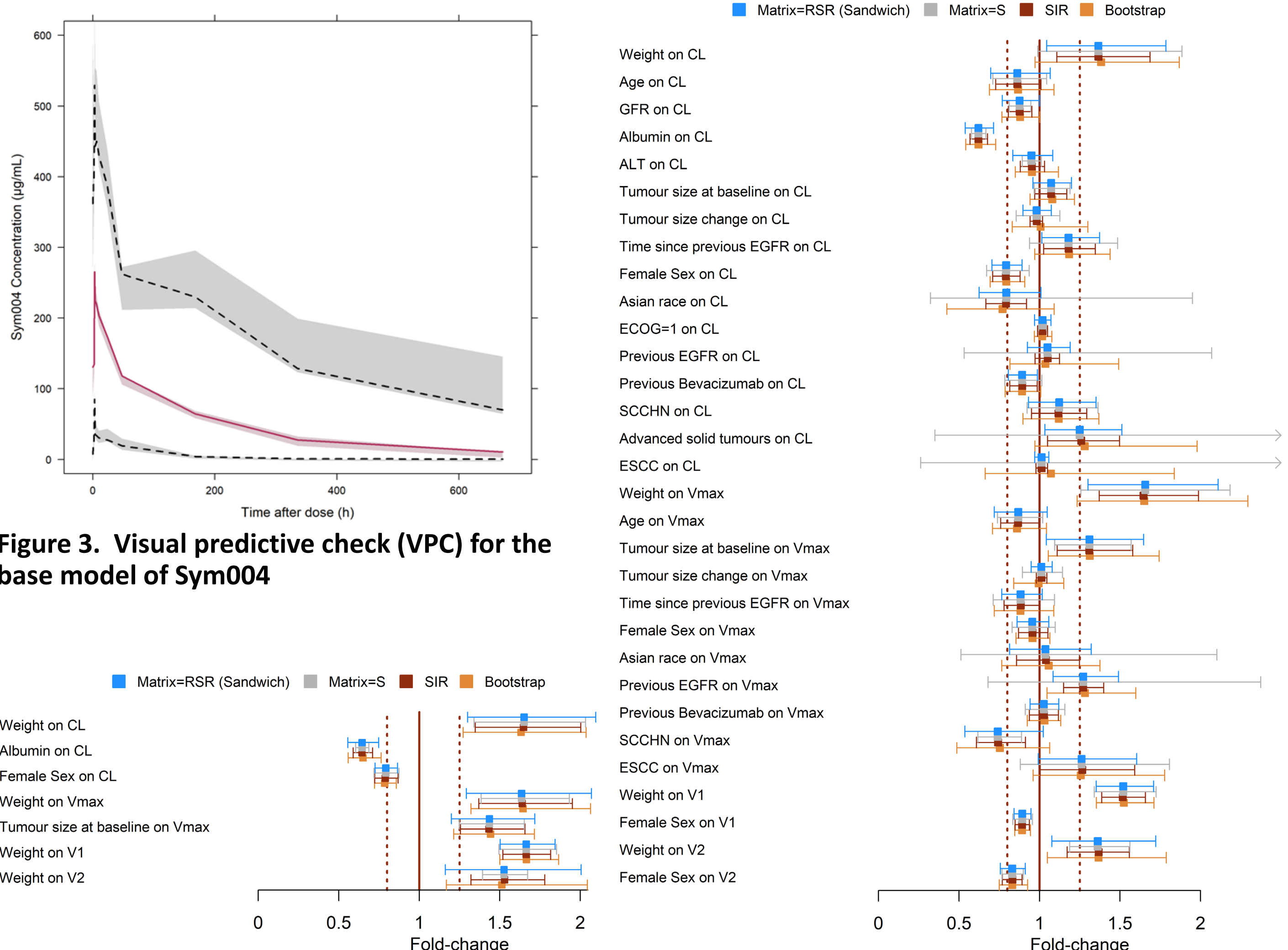


Figure 3. Visual predictive check (VPC) for the base model of Sym004

Figure 5. Forest plot reduced covariate model

Figure 4. Forest plot full covariate model

Table 1. Parameter estimates for the reduced covariate model for Sym004

Parameter	Estimate (95% CI)	CV
V1 (mL)	3450 (3370/3530)	1.2%
V2 (mL)	2410 (2260/2570)	3.3%
CL (mL/h)	14.1 (13.2/15.1)	3.4%
CL2 (mL/h)	33.0 (28.9/37.1)	6.3%
Vmax (µg/h)	1270 (1170/1370)	4.0%
Km (µg/mL)	3.92 (2.56/5.29)	17.7%
Proportional error (fraction)	0.174 (0.162/0.186)	3.6%
Additive error (µg/mL)	2.87 (1.64/4.09)	21.8%
Weight on Vmax, fold-change across 95% of weight range	1.64 (1.29/2.07)	24.4%
Weight on V1, fold-change across 95% of weight range	1.66 (1.50/1.84)	10.2%
Weight on V2, fold-change across 95% of weight range	1.53 (1.16/2.01)	32.9%
Weight on CL, fold-change across 95% of weight range	1.65 (1.30/2.10)	24.3%
Female Sex on CL, fold-change relative to males	0.792 (0.726/0.865)	19.3%
Albumin on CL, fold-change across 95% of albumin range	0.645 (0.557/0.747)	17.1%
Tumour size at BL on Vmax, fold-change across 95% of tumour size range	1.44 (1.20/1.72)	25.3%

Etas	IIV	Shrinkage
Vmax	22.2%	31.9%
V1	18.9%	15.0%
CL	27.3%	21.1%

Parameter definitions, see Figure 1. SEs by the sandwich method. BL=baseline, tumor size: sum of diameters of target lesions by Recist 1.1

Conclusions

The full covariate model for Sym004 indicated that liver and kidney function, race, age and prior therapy with anti-EGFRs did not affect the Sym004 PK properties in a clinically relevant manner.

The reduced covariate model indicated that four covariates may be clinically relevant for Sym004 exposure based on the 0.8-1.25 limits, but these limits warrant further support via PK/PD modelling.

For full covariate models, which may be over-parameterised and present computational difficulties, care should be taken choosing the method for calculation of SE. Resorting to the simpler MATRIX=S instead of the sandwich estimator to mitigate the computational difficulties, may result in inflated SE estimates if the model is over-parameterised.

Too wide confidence intervals may give inconclusive results about the clinical relevance of the covariates in the FCM, and could influence deleting covariates to obtain a reduced covariate model.

If the sandwich method is not feasible and simplification of the covariate model is not warranted, the SIR method seems to result in the most robust SE estimation in the FCM.

References

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