

Evaluation of Variance-based Global Sensitivity Analysis for Covariate Effects

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Introduction

- Understanding a contribution of each covariate effect to an interested metric (e.g. $C_{\max}$, AUC) is important to assess an impact of each covariate effect, e.g., for dose adjustment based on the covariates.
- A variance of inter-individual variability (IIV) for the metric is considered to be variances from individual covariates and from individual random variables which are defined as ETA in NONMEM [1].
- Variance ratios using global sensitivity analysis approach [2, 3] can be useful to efficiently assess the contribution of each covariate effect and each random effect on the metric.

Objectives

In this study, the contribution of covariate effect and random effect on the metric was evaluated based on the variance ratios using global sensitivity analysis approach for assessment of impact of each covariate effect.

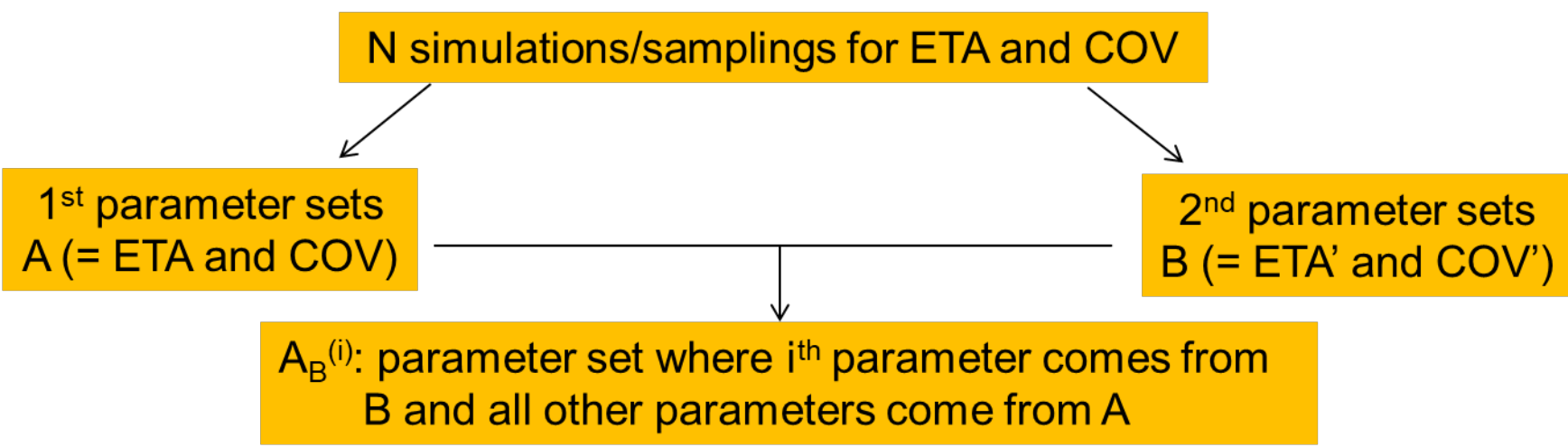
Methods

- Monte-Carlo simulations were conducted to simulate individual covariates and ETAs, and calculate individual outputs for an metric based on the simulated covariates and ETAs.
- A sensitivity index based on the following variance ratios were used to evaluate the contribution of covariate effect and random effect.

$$\text{Sensitivity index} = \frac{\text{Variance explained by each covariate or ETA}}{\text{Overall variance for metric}}$$

- Soboljansen* in R library "sensitivity" was used [4]. The scheme of algorithm as follows:

Scheme of algorithm in soboljansen for variance of output contributed with i^{th} variable X_i



$$\begin{aligned} \text{Variance of } X_i \text{ for 1st order effect} \\ V_{X_i}(E_{X \sim i}(Y|X_i)) &= V(Y) - \frac{1}{2N-1} \sum_{j=1}^N \left(f(B)_j - f(A_B^{(i)})_j \right)^2 \\ \text{Variance of } X_i \text{ for total order effect} \\ V_{X_i}(E_{X \sim i}(Y|X_i)) &= \frac{1}{2N-1} \sum_{j=1}^N \left(f(A)_j - f(A_B^{(i)})_j \right)^2 \end{aligned}$$

COV: Covariate
N: Number of simulations/samplings
X: Variables composed of individual COV and ETA
Y: Individual outputs for metric

- The sensitivity index was calculated from each of 1st order effect and total order effect as follows:

$$S_i = \frac{V_{X_i}(E_{X \sim i}(Y|X_i))}{V(Y)}$$

- Models in the below table were tested for assessment of sensitivity index.

Model #	Model description	Key parameter	Output
Model 1	Oral 1-compartment PK model with mono-exponential covariate models and without ETAs	CL/F = 0.693*exp(COV1); V/F = 1*exp(COV2) KA = 5*exp(COV3) IIV for covariate: CV 30% for COV1/COV2/COV3	Steady-state $C_{\max}$ and time above 2 mg/L of target concentration ($T_{>C=2}$)
Model 2 [5]	Lusutrombopag PK/PD model (oral 3-compartment PK model and 5-compartment PD model)	CL/F = 0.775*(WT/66.2) ^{0.710} *exp(ETA _{CL}) V2/F = 13.7*(WT/66.2) ^{1.02} *exp(ETA _{V2}) V3/F = 8.41*(WT/66.2)*exp(ETA _{V3}) KA = 0.299*exp(ETA _{KA}); KM = 0.0302*exp(ETA _{KM}) EC50 = 80.9*exp(ETA _{EC50}); PLT0 = 20.2*exp(ETA _{PLT0}) IIV for ETA and covariate: CV 10~20% for ETA _{CL} /ETA _{V2} /ETA _{V3} /ETA _{PLT0} CV 30~50% for ETA _{KA} /ETA _{KM} /ETA _{EC50} WT: random sampling from original dataset	Peak platelet count
Model 3 [6]	Lusutrombopag QSP model (44-component model)	CL/F = 0.775*(WT/70) ^{0.710} *exp(ETA _{CL}) V2/F = 13.7*(WT/70) ^{1.02} *exp(ETA _{V2}) V3/F = 8.41*(WT/70) ^{1.06} *exp(ETA _{V3}) EC50 = 183*exp(ETA _{EC50}); PLT0 = 20.1*exp(ETA _{PLT0}) TPO = 1.4*exp(ETA _{TPO}); PP = 2500*exp(ETA _{PP}) IIV for ETA and covariate: CV 10~20% for ETA _{CL} /ETA _{V2} /ETA _{V3} /ETA _{PLT0} /ETA _{TPO} /ETA _{PP} /Wt ³ ; CV 30% for ETA _{KA} ; CV 50% for ETA _{EC50}	Peak platelet count

COV1, COV2, COV3, and ETA were assumed to be according to normal distribution with mean of zero.
a mean and CV of WT were 66.2 and 20%, respectively.
WT = body weight; TV = Typical value; IIV = inter-individual variability; KM = rate constant for platelet maturation;
EC50 = 50% effective concentration; PLT0 = baseline platelet count; QSP = quantitative systems pharmacology;
TPO = baseline thrombopoietin level; PP = platelet number produced in one megakaryocyte; q24h = every 24 hours
Unit: L/hr for CL/F; L for V/F, V2/F, and V3/F; hr⁻¹ for KA and KM; ng/mL for EC50; *10,000/ μ L for PLT0; pM for TPO

Conclusion

- The contribution of each covariate effect to the metric was quantified using the sensitivity index based on variance ratios.
- The variance-based global sensitivity analysis would be proposed as an efficient approach to assess the impact of covariate effect for pharmacometric models and quantitative systems pharmacology models.

Results

Model 1 (Oral 1-compartment model)

- The variance ratios demonstrated the variability for $C_{\max}$ was highly dependent on the covariate on V/F, and the variability for $T_{>C=2}$ was highly dependent on the covariate on CL/F (Figure 1, left).
- These results were consistent with visual inspections based on the simulated concentration profiles (Figure 1, right).

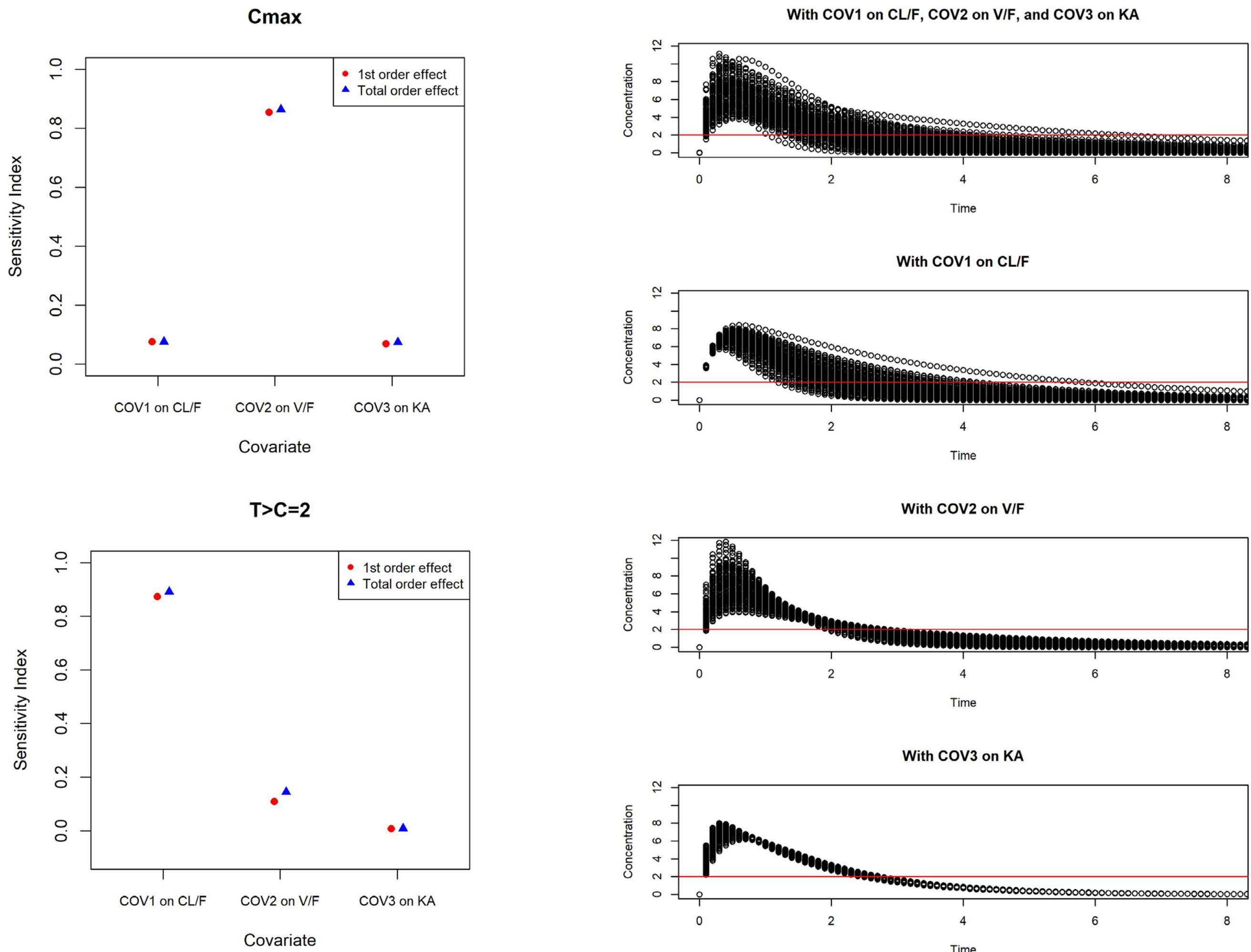


Figure 1 Sensitivity index for $C_{\max}$ or $T_{>C=2}$ for Model 1 (left) and PK Profiles with each of 3 parameter-covariate models (right). 10-mg dose every 24 hours. Solid lines in the right figures present the concentration of 2 mg/L.

Model 2 (Lusutrombopag PK/PD model)

- Simulated platelet counts are shown in Figure 2, left.
- The variability for peak platelet count was derived from ETAs of 50% effective concentration (EC50) and ETAs of baseline platelet count (Figure 2, right).
- Body weight did not affect the variability for peak platelet counts, although body weight was an influential factor for the exposure of lusutrombopag.

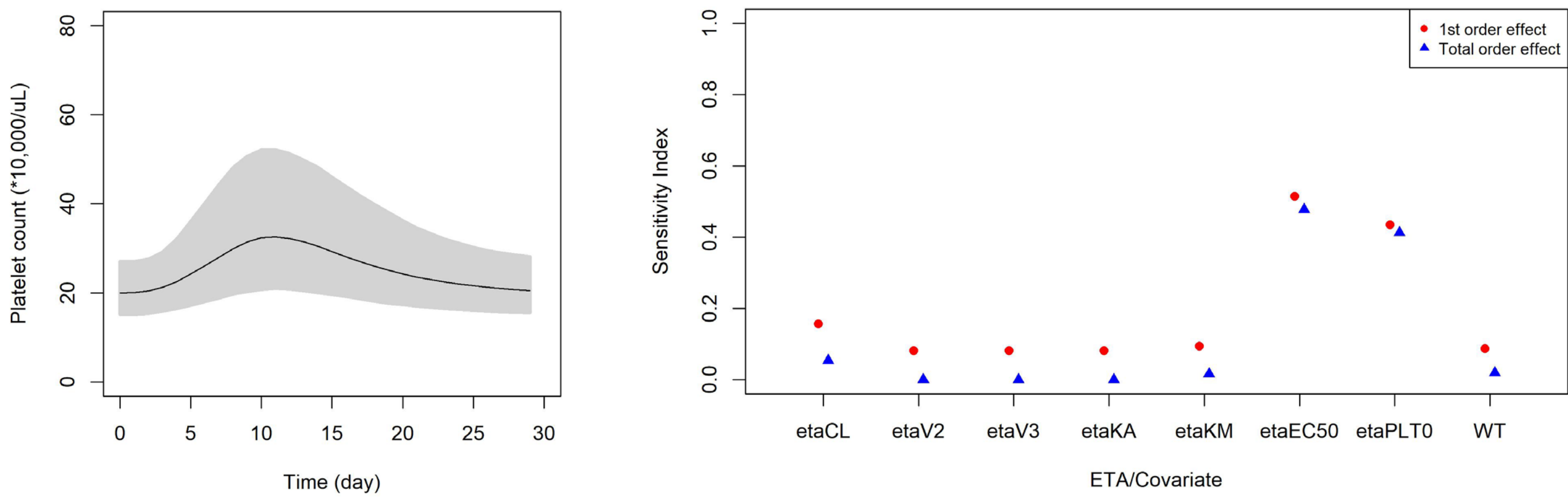


Figure 2 Simulated platelet counts for Model 2 (left) and sensitivity index for peak platelet counts (right). 1-mg dose every 24 hours for 7 days.

Model 3 (Lusutrombopag QSP model)

- Simulated platelet counts are shown in Figure 3 (left).
- The variability for peak platelet count was derived from ETAs of EC50 and ETAs of baseline platelet count (Figure 3, right). This result was consistent with that for Model #2 (PK/PD model).

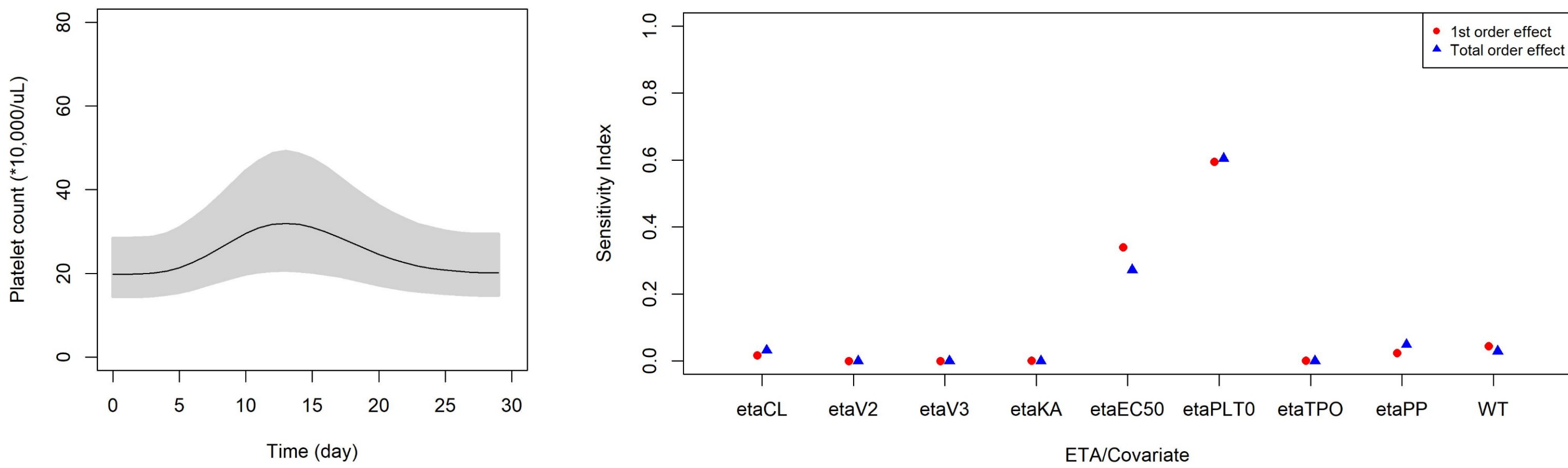


Figure 3. Simulated platelet counts for Model 3 (left) and sensitivity index for peak platelet counts (right). 1-mg dose every 24 hours for 7 days.

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