

Continuous Time Markov Modelling in Systemic Lupus Erythematosus



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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an autoimmune disease that can affect multiple organs, including skin and kidney. Vobarilizumab, a half-life extended anti-IL6R NANOBODY® drug was tested clinically as a treatment for SLE. This study was a 48-week, randomized, double-blind, placebo-controlled, dose-range finding phase II study of Vobarilizumab administered subcutaneously on top of standard of care in subjects with moderate to severe active, seropositive SLE. In the study, the efficacy, safety, pharmacokinetics, pharmacodynamics, immunogenicity, flare rate, steroid reduction and health-related quality of life, with different dose regimens of Vobarilizumab were assessed. SLEDAI-2K (Systemic Lupus Erythematosus Disease Activity Index 2000) and BILAG (British Isles Lupus Assessment Group) disease activity scores were determined every 4 weeks. mSRI (modified SLE Responder Index¹, based on SLEDAI-2K and BILAG scores, omitting complement score compared to SRI) was analyzed as response criterium for this analysis. The aim of the present study is the development of a model to provide an accurate description of the mSRI data and their time course as well as the probability of dropout, treatment failure and missing mSRI records over time.

DATA EXPLORATION

The mSRI responder index data categorize each subject from most severe to least severe disease state as mSRI-4 Non-Responder (NR), mSRI-4 responder, mSRI-5 responder or mSRI-6 responder. Considering the small difference between mSRI-5 and mSRI-6 response rates (Figure 1), these categories were both considered as mSRI-5 responders in this analysis. The primary endpoint of the study – dose response in the modified BILAG-based combined lupus assessment (mBICLA)² at week 24 – was not met³ and visual inspection of the mSRI data did not reveal a clear dose-response relationship (Figure 1). The majority of the subjects had less than 3 transitions in their recorded mSRI responses during their study participation.

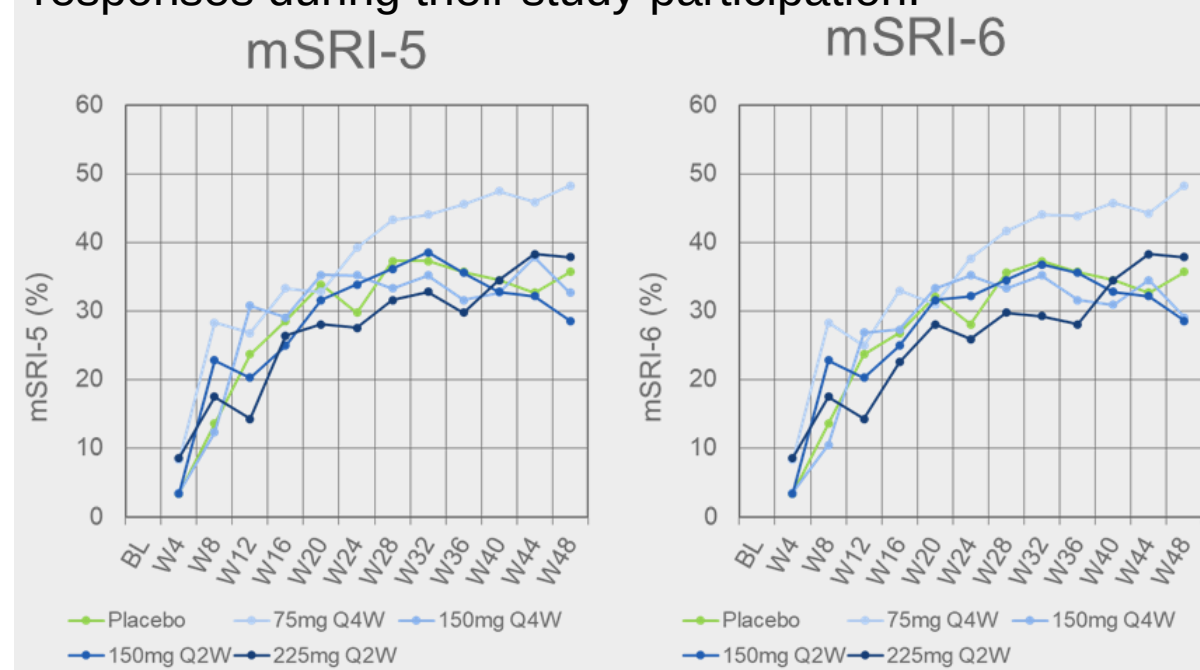
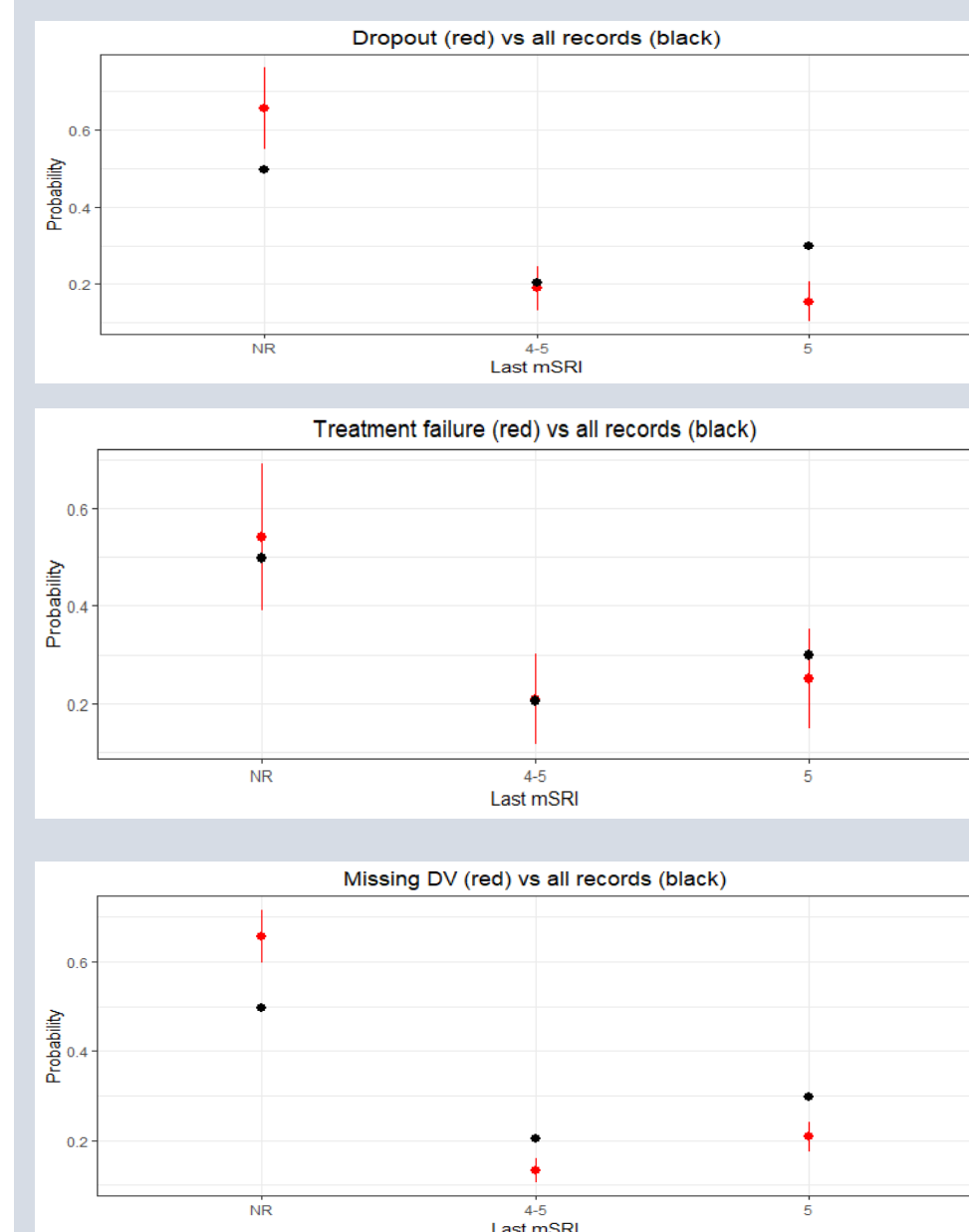


Figure 1. Overview of the percentage of mSRI-5 (left) and mSRI-6 (right) responders over time in the different treatment groups.

MISSING DATA



mSRI response data was missing in the dataset either because of treatment failure (i.e. more than protocol-allowed increase in immunosuppressives, antimalarials or corticosteroids), dropout of the subject or because of a missed observation. Informativeness of the missing data was investigated by comparing the distribution of mSRI response in the previous observation before a missing record with the overall distribution of mSRI responses.

- Out of 304 subjects, there were 57 dropouts (19%) and 24 treatment failures (8%).
- Out of 2918 observation records, there were 186 missing observations (6%).

Figure 2. Overview of the fraction for which the previous observation was mSRI non-responder (NR), mSRI-4 but not mSRI 5 responder and mSRI 5 responder for all observations (black), or missing data (red) Top: dropout, middle: treatment failure, bottom: missing observation. Vertical lines: standard deviations calculated as square root of the count value.

METHODS

A continuous time Markov Model was developed to describe the mSRI data using the Laplacian estimation method in ADVAN6 in NONMEM 7.3. This model was based on published modelling of American College of Rheumatology's (ACR) response scores in Rheumatoid Arthritis patients.⁴ A schematic representation of the structural model is given in Figure 3 and the structural model equations are given in equation 1-3. Missing data models were developed separately by directly estimating the probability of each type of missingness on logit scale, with the constraint that the sum of all missingness probabilities and the probability of non-missing data equals 1. IIV was implemented as multiplication with an exponentiated normal distribution for rate constants and as addition with a normal distribution for the logit of missing data probabilities.

$$\text{Equation 1: } \frac{dP_0}{dt} = k_{01}P_1 - k_{10}P_0$$

$$\text{Equation 2: } \frac{dP_1}{dt} = -k_{01}P_1 + k_{10}P_0 - k_{21}P_1 + k_{12}P_2$$

$$\text{Equation 3: } \frac{dP_2}{dt} = k_{21}P_1 - k_{12}P_2$$



Figure 3. Schematic representation of the structural model

Model development: Model changes were evaluated numerically based on the objective function value (OFV), the relative standard error (RSE) of the parameter estimates and the shrinkage on the IIV parameters, and visually based on a Visual Predictive Check (VPC) and customized residual plots: To evaluate accuracy, the expected mSRI value on a scale of 1 to 3 (1 = mSRI 4 NR, 2 = mSRI 4 but not 5 responder, 3 = mSRI 5 responder) was calculated by multiplying each of those mSRI scores with the model-predicted probability for that score. The observed mSRI score was subtracted from this expected value and used as a residual for accuracy. To evaluate precision, the model-predicted probability for the observed mSRI score was used directly. Both values were calculated for observations and simulation and their means and confidence intervals were plotted over time.

Covariate testing: Potential covariates were explored graphically on the transition rate constants between mSRI response compartments and on the probabilities of missing data. The strongest correlations based on graphical analysis and correlation coefficients were tested for significance with a threshold of 0.01 using the likelihood ratio test. Two exposure metrics derived from previous PK modelling were tested as covariates (independent on graphical analysis) on the transition rate constants as linear, sigmoidal or bell-shaped exposure response relationships.

RESULTS

Model development resulted in a structural model as shown in figure 3 with Inter-Individual Variability (IIV) on k_{21} and on the missing DV probability. A linear and identical impact of time on k_{21} and k_{12} was included as well as a step-wise impact of time on the missing DV probability. The previous mSRI response was included as covariate on both the dropout and the missing DV probability by estimating separate probabilities for all three possibilities of the previous mSRI response. In addition, both the region and the baseline modified SLEDAI-2K score were included as covariates on k_{21} .

Fixed structural & subject random effects					Covariate effects			
Description	Unit	Estimate	RSE (%)	Shrinkage (%)	Description	Unit	Estimate	RSE (%)
k_{10}	day ⁻¹	0.0091	8		$T_{k_{21}+k_{12}}$	day ⁻²	-0.0022	19
k_{01}	day ⁻¹	0.0076	13		$\max(T_MIS)$	-	-0.249	20
k_{21}	day ⁻¹	0.0151	24		T_{50_MIS}	day	63.1	2
k_{12}	day ⁻¹	0.0131	31		V_MIS		60	Fixed
DO_NR	%	2.53	5		DO_mSRI4-5	%	1.69	8
MIS_NR	%	0.676	9		DO_mSRI 5	%	0.947	8
TF_NR	%	0.777	4		MIS_mSRI 4-5	%	0.257	11
IIV_ k_{21}	ω^2	3.19	35	34	MIS_mSRI 5	%	0.228	10
IIV_MIS	ω^2	4.42	31	38	LATA_ k_{21}		7.86	54
					BMSL_ k_{21}	day ⁻¹	0.122	82

DO = Dropout probability, MIS = Missing mSRI record probability at time 0, TF = Treatment failure probability, IIV = Inter Individual Variability, RSE = Relative Standard Error, $T_{k_{21}+k_{12}}$ correlation coefficient between time and rate constant k_{21} and k_{12} , $\max(T_MIS)$ = maximal effect of time on MIS, T_{50} = Time at which the half-maximal effect is reached; γ = hill slope; NR = mSRI-4 non-responders at previous observation, mSRI4-5 = mSRI-4 but not mSRI-5 responders at previous observation, mSRI5 = mSRI-5 responders at previous observation; LATA_ k_{21} = Region Latin America impact on k_{21} , estimated relative to the k_{21} for other regions; BMSL_ k_{21} = Baseline modified SLEDAI-2K score > 10 impact on k_{21} , estimated as additive parameter to k_{21} for lower baseline modified SLEDAI-2K scores.

The developed model was able to describe the development of mSRI and missing data categories over time as indicated by (dose stratified) VPCs (figure 4, figure 5 and figure 6). The IIV was also well captured as indicated by the frequency distribution of mSRI transitions (figure 7) and by the customized residual distribution plots for accuracy (figure 8) and precision (figure 9).

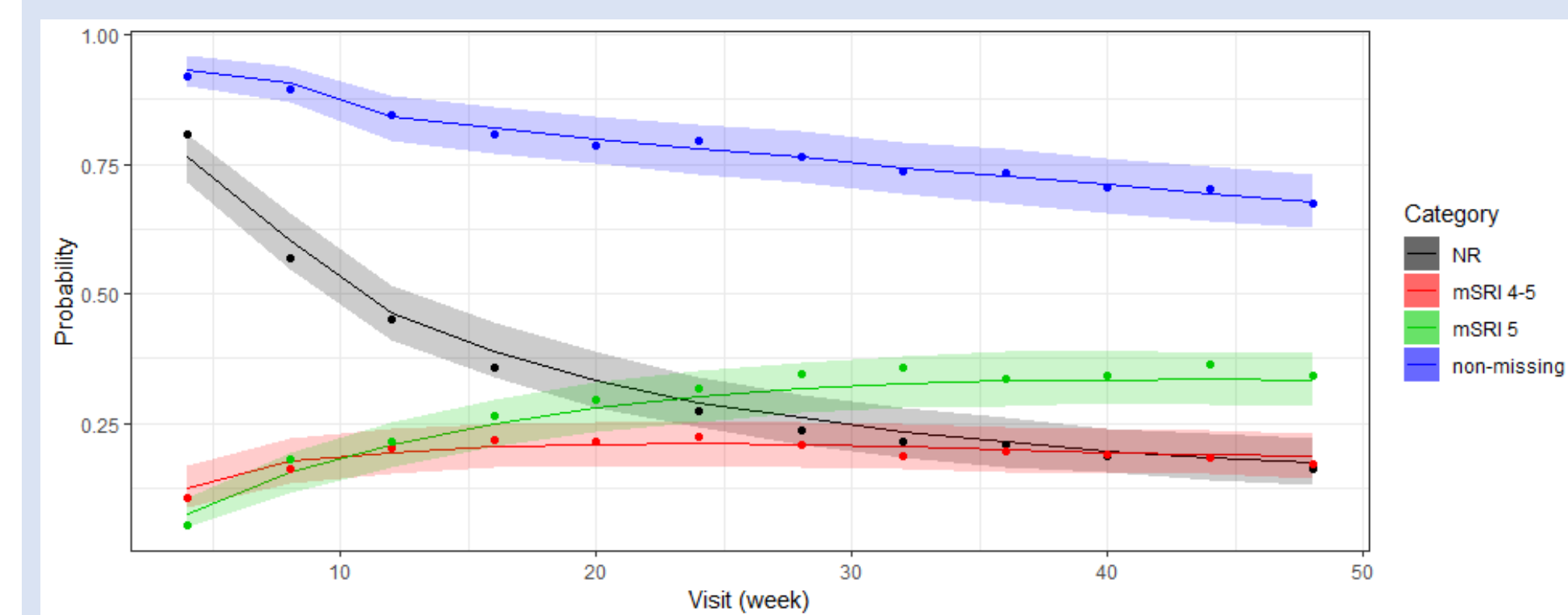


Figure 4. VPC of mSRI response rates in the final model. Observed fraction of mSRI responders per visit as dots, median simulated fraction of responders as lines and 95% prediction interval as shaded areas. The fractions are calculated as the fraction of the total population with at least one observation in the dataset.

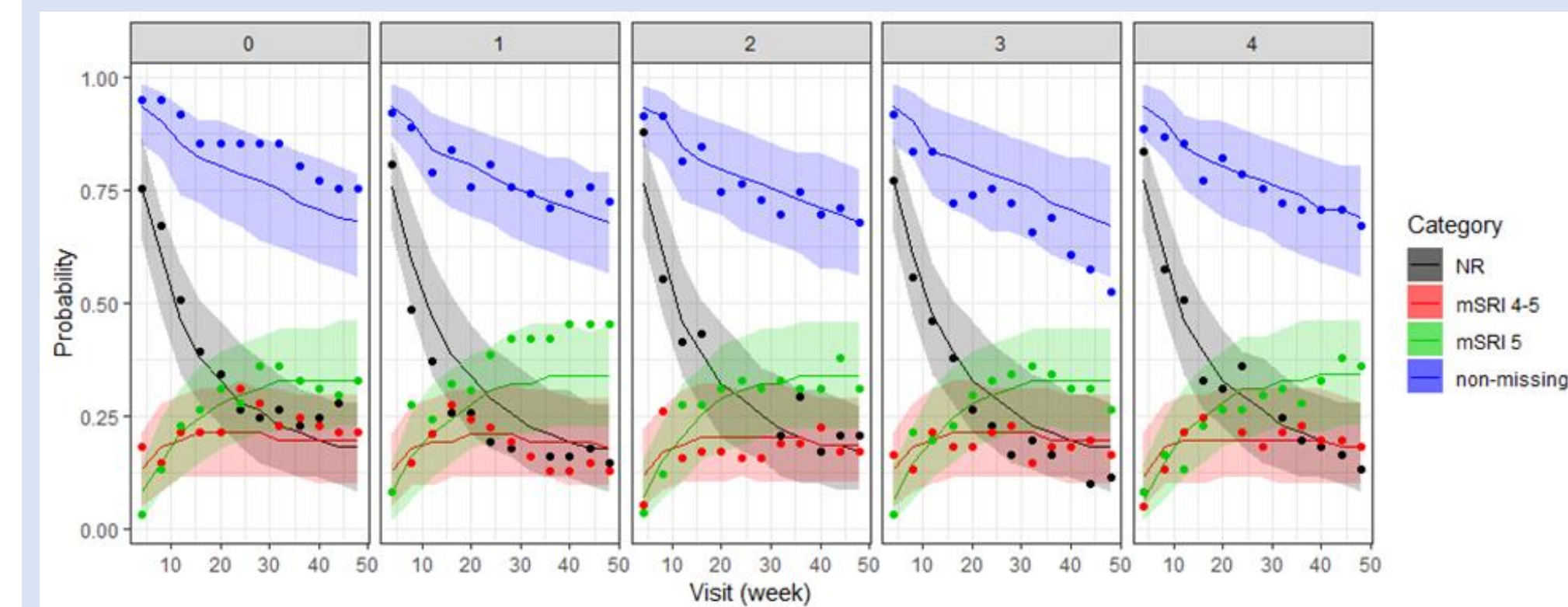


Figure 5. Dose-group stratified VPC of mSRI response rates in the final model. Observed fraction of responders per visit as dots, median simulated fraction of responders as lines and 95% prediction interval as shaded areas. The fractions are calculated as the fraction of the total population per dose group with at least one observation in the dataset. Dose group 0 = placebo, 1 = 75 mg Q4W, 2 = 150 mg Q4W, 3 = 150 mg Q2W, 4 = 225 mg Q2W.

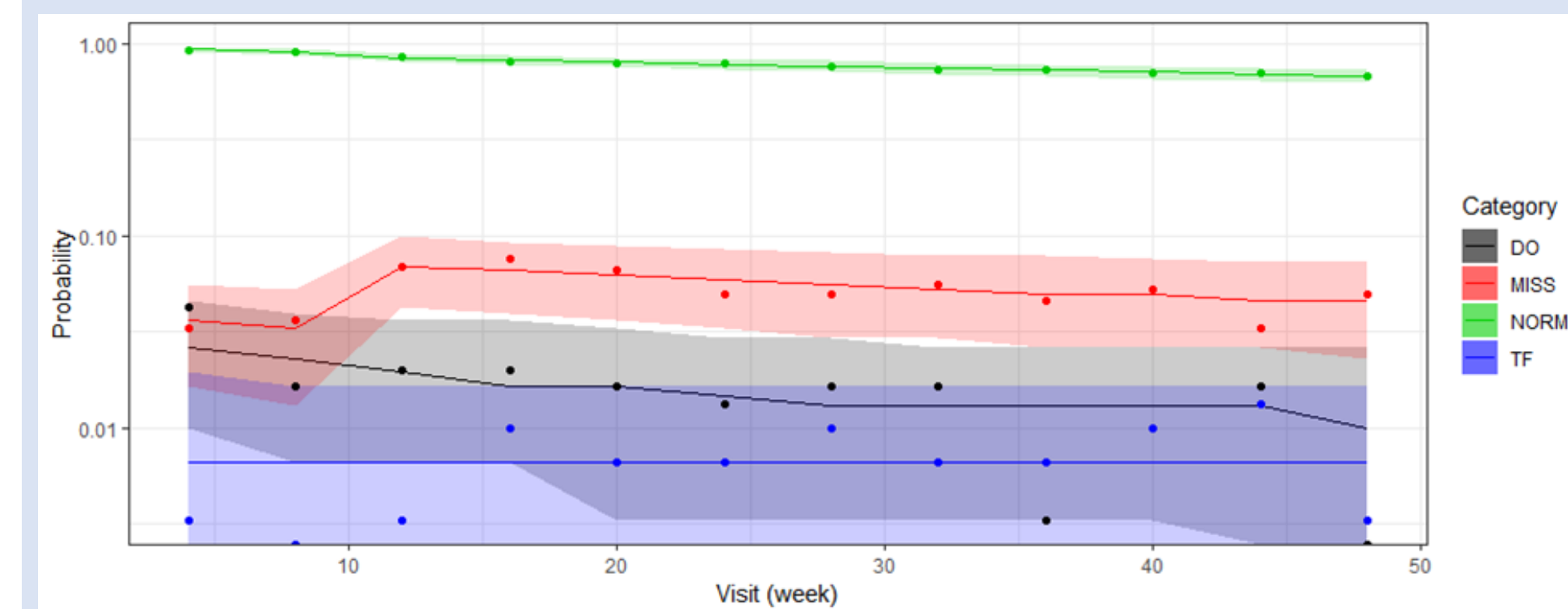


Figure 6. VPC of missing data in the final model. Observed fraction of missing data per visit as dots, median simulated fraction of missing data as lines and 95% prediction interval as shaded areas. The fractions are calculated as the fraction of the total population with at least one observation in the dataset. DO = dropout, MISS = missing mSRI record, NORM = non-missing, TF = treatment failure.

CONCLUSIONS

The developed model provided an accurate description of the mSRI data and their time course as well as the probability of dropout, treatment failure and missing mSRI records over time. Time was included as covariate on both k_{21} and the probability of missing mSRI records, last observed mSRI score was included as covariate for the probability of missing mSRI records and dropout, Latin America as region and a baseline modified SLEDAI-2K score > 10 were included as covariates on k_{21} . No exposure-response or dose-response relationship could be identified. Customized residual plots for accuracy and precision allowed for an improved analysis of IIV model performance and its trend over time.

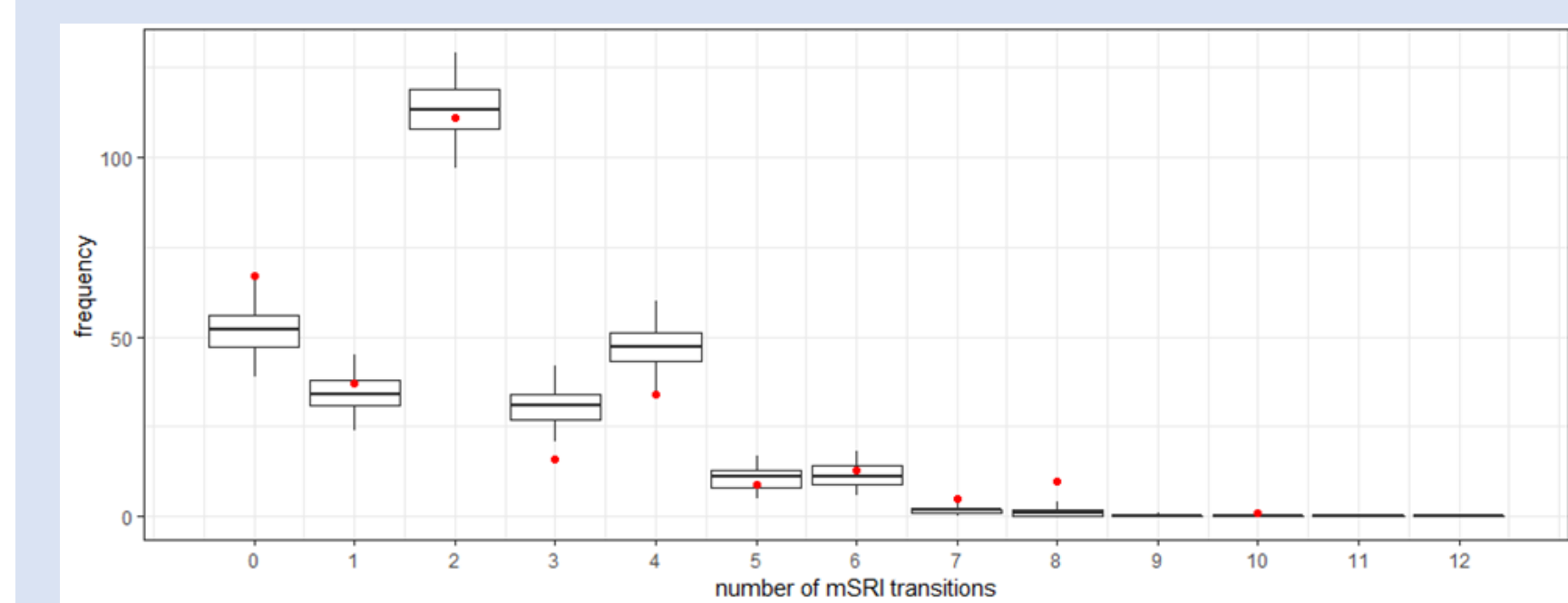


Figure 7. VPC of the distribution of observed numbers of mSRI transitions per patient. Red dots indicate the observed number of patients with the corresponding number of mSRI transitions. Boxplots indicate the distribution of simulated numbers of mSRI transitions with median as black line, 50% prediction interval within the box and 95% prediction interval between the whisker ends. See “missing data” section for definition of the mSRI transition count

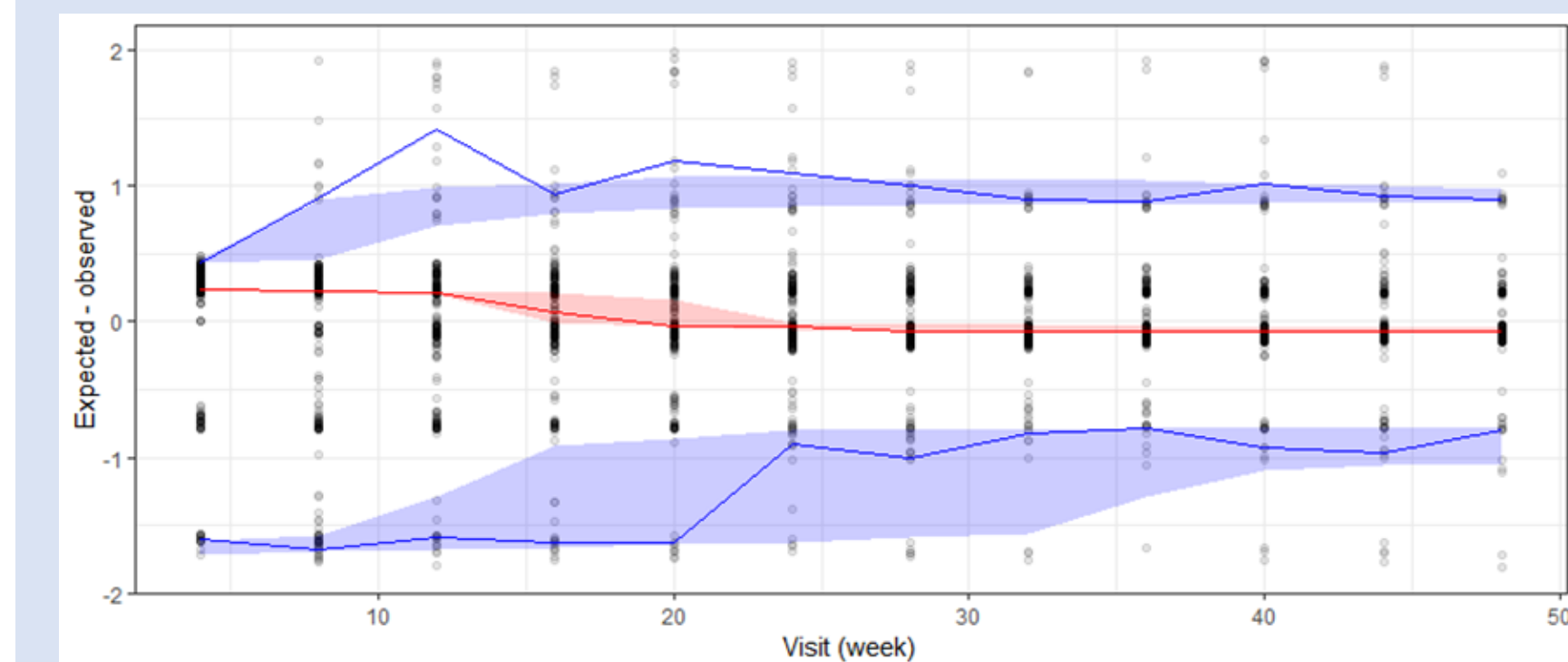


Figure 8. VPC of the model accuracy compared to simulated and observed data. The dots indicate the observed data, the red line the median of the observed data and the blue lines the 95% confidence interval of the data. The shaded areas indicate the 90% prediction interval around the simulated median and 95% confidence interval.

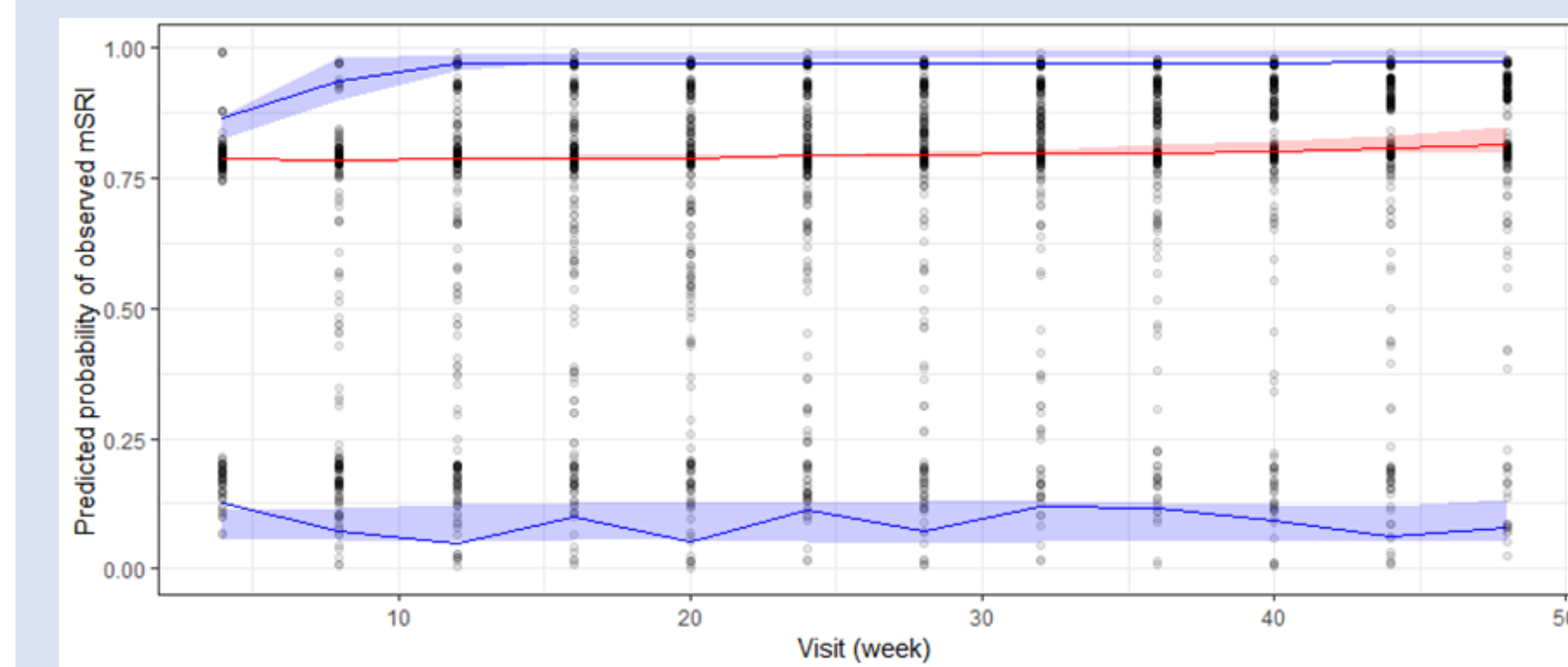


Figure 9. VPC of the model precision compared to simulated and observed data. The dots indicate the observed data, the red line the median of the observed data and the blue lines the 95% confidence interval of the data. The shaded areas indicate the 90% prediction interval around the simulated median and 95% confidence interval.

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