

A population pharmacokinetic and exposure-response model of golimumab for targeting endoscopic remission in patients with ulcerative colitis

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Background

- **Golimumab** (GLM, Simponi®) is a fully human anti-tumour necrosis factor-alpha monoclonal antibody for the treatment of patients with moderately to severely active ulcerative colitis (UC).
- **Endoscopic remission** (ER; a decrease in Mayo endoscopic subscore [MES] from 3 [severe disease] or 2 [moderate disease] at baseline to 1 [mild disease] or 0 [inactive disease] at week 14) has been focused as a therapeutic target in patients with UC.¹
- Higher **serum trough concentrations** (TC) of GLM six weeks after start of therapy were associated with a greater proportion of patients achieving ER.²

Objectives

- To develop an **exposure-response model** that links GLM exposure metrics (TC and cumulative area under the concentration-time curve [CAUC]), derived from a **population pharmacokinetic model**, to probabilities of transitioning between MES states from baseline to week 14.

Methods

Data source					
Number of patients:	56 patients				
Study centers:	- University Hospitals Leuven, Belgium (2 studies, n = 10, 19)³⁻⁴ - Ljubljana University Medical Centre, Slovenia (1 study, n = 27)⁵				
Dosing scheme:	The diagram illustrates the dosing schedule over 14 weeks. Induction treatment is administered from week 0 to week 6, and maintenance treatment is administered from week 6 to week 14. The timeline is marked with vertical lines at weeks 0, 2, 6, 10, and 14.				
Time (weeks):	0	2	6	10	14
Dose (mg):					
< 80 kg	200	100	50	50	50
≥ 80 kg	200	100	100	100	100
Sample collection:	baseline, intermediate, trough samples				
Sampling technique:	peripheral venepuncture (VP) samples, dried blood spot (DBS) samples				
Efficacy evaluation:	MES at baseline and week 14				

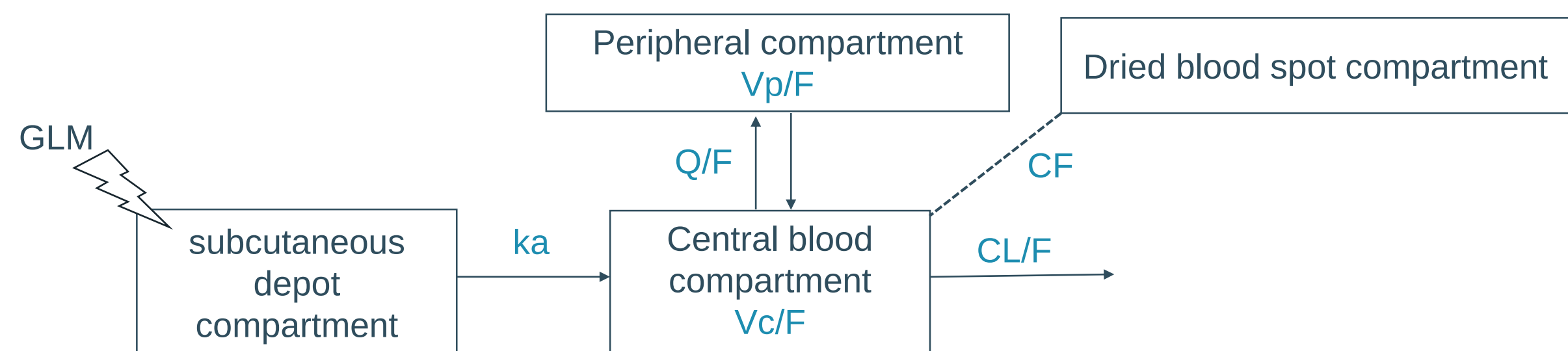
Population pharmacokinetic model development

Software:	NONMEM (version. 7.4)
Method:	first-order conditional estimation with interaction (FOCE+I)
Covariate analysis:	stepwise covariate modelling (forward $\alpha = 0.010$, backward $\alpha = 0.001$)
GLM concentration-time data:	VP samples (n = 414) and DBS samples (n = 296) ⁶

Exposure-response model development⁷

Model:	Markov model
Assumptions:	• only ordered transitions can occur • transition probabilities between states can be inversed

Population pharmacokinetic model:



Exposure-response model:

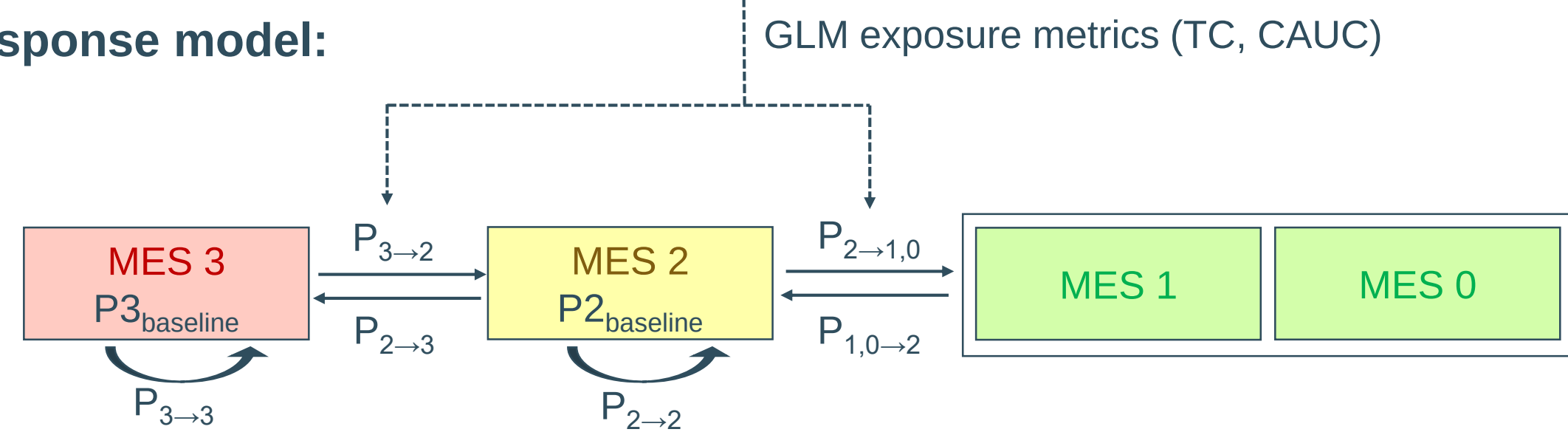


Figure 1. Scheme of population pharmacokinetic and exposure-response models

Table 1. Estimated parameters of population pharmacokinetic and exposure-response models

Parameter	Estimated value	%RSE [%Shrinkage]	SIR estimate ⁸	[SIR 95% CI]
Population pharmacokinetic model				
ka, absorption rate constant (day ⁻¹)	0.495	15	0.501	[0.417 – 0.596]
CL/F, apparent clearance (L/day)				
when no antibodies to GLM	0.417	9	0.413	[0.370 – 0.464]
when antibodies to GLM	0.545	11	0.541	[0.464 – 0.627]
Vc/F, apparent volume of distribution in central blood compartment (L)	8.82	8	8.88	[7.79 – 9.83]
Q/F, apparent intercompartmental clearance (L/day)	0.469	20	0.461	[0.368 – 0.587]
Vp/F, apparent volume of distribution in peripheral compartment (L)				
when no previous biological therapy	3.85	43	3.93	[3.03 – 5.18]
when previous biological therapy	15.3	43	15.2	[8.48 – 31.0]
CF, dried blood spot-to-venepuncture conversion factor	4.14	3	4.14	[3.95 – 4.34]
Interindividual variability				
CL/F (%)	56.6	13 [4]	57.1	[45.0 – 71.8]
Vc/F (%)	28.3	16 [14]	28.6	[22.4 – 36.1]
Vp/F (%)	220.7	22 [21]	240.4	[133.7 – 419.8]
correlation(CL/F-Vc/F) (%)	37.9	43	37.2	[13.7 – 64.1]
correlation(CL/F-Vp/F) (%)	-43	31	-43.5	[-64.1 – -16.8]
correlation(Vc/F-Vp/F) (%)	48.6	32	48.3	[21.6 – 72.5]
Residual errors				
VP sample				
proportional error (%)	2.62	20 [7]	2.61	[1.74 – 3.66]
additive error (mg/L)	0.874	34 [7]	0.886	[0.650 – 1.117]
DBS sample				
proportional error (%)	6	6 [7]	6.04	[4.79 – 7.17]
additive error (mg/L)	0.059	104 [7]	0.06	[0.025 – 0.136]
Exposure-reponse model				
TC at week14.50 ^{3→2} (mg/L)	0.5	48	0.5	[0.2 – 1.0]
TC at week14.50 ^{2→1.0} (mg/L)	4.1	36	4.2	[2.0 – 8.1]
RSE, relative standard error; SIR, sampling importance resampling; CI, confidence interval				
TC at week14.50 ^{3→2} , predicted GLM TC at week 14 (TC at week14) corresponding to a 50% probability of going from MES 3 to 2				
TC at week14.50 ^{2→1.0} , predicted GLM TC at week 14 (TC at week14) corresponding to a 50% probability of going from MES 2 to 1 or 0				

Conclusion

Our exposure-response model allows dose selection for targeting a certain golimumab exposure and the associated probability of endoscopic remission.

Results

- Data were described by a two-compartment model with linear absorption and elimination (**Figure 2**).
- The CL/F was 31% higher in patients when antibodies to GLM were present. Patients who had previously received biologicals had a 4-fold higher Vp/F. The unexplained interindividual variability remained large after the introduction of the two covariates (57% and 221% for CL/F and Vp/F, respectively) (**Figure 3**).
- A total of 14/40 patients (35%, 16/56 had no endoscopy data available) achieved ER.
- A GLM TC at week 14 was the best predictor of ER (**Table 1**).
- Targeting the patients in our cohort (55% and 45% at MES 3 and 2 at baseline, respectively) to the TC of 3.2 mg/L at week 14 (ROC analysis) predicted a 41% probability of achieving ER (**Figure 4**):

$$0.55 \times [(3.2/0.5)/(1+(3.2/0.5)) \times (3.2/4.1)/(1+(3.2/4.1))] + 0.45 \times [(3.2/4.1)/(1+(3.2/4.1))] \\ = 0.55 \times 0.38 + 0.45 \times 0.44 = 0.41.$$

Patients with MES at baseline of 3 and 2 had a 38% and 44% chance for achieving ER at w14, respectively.

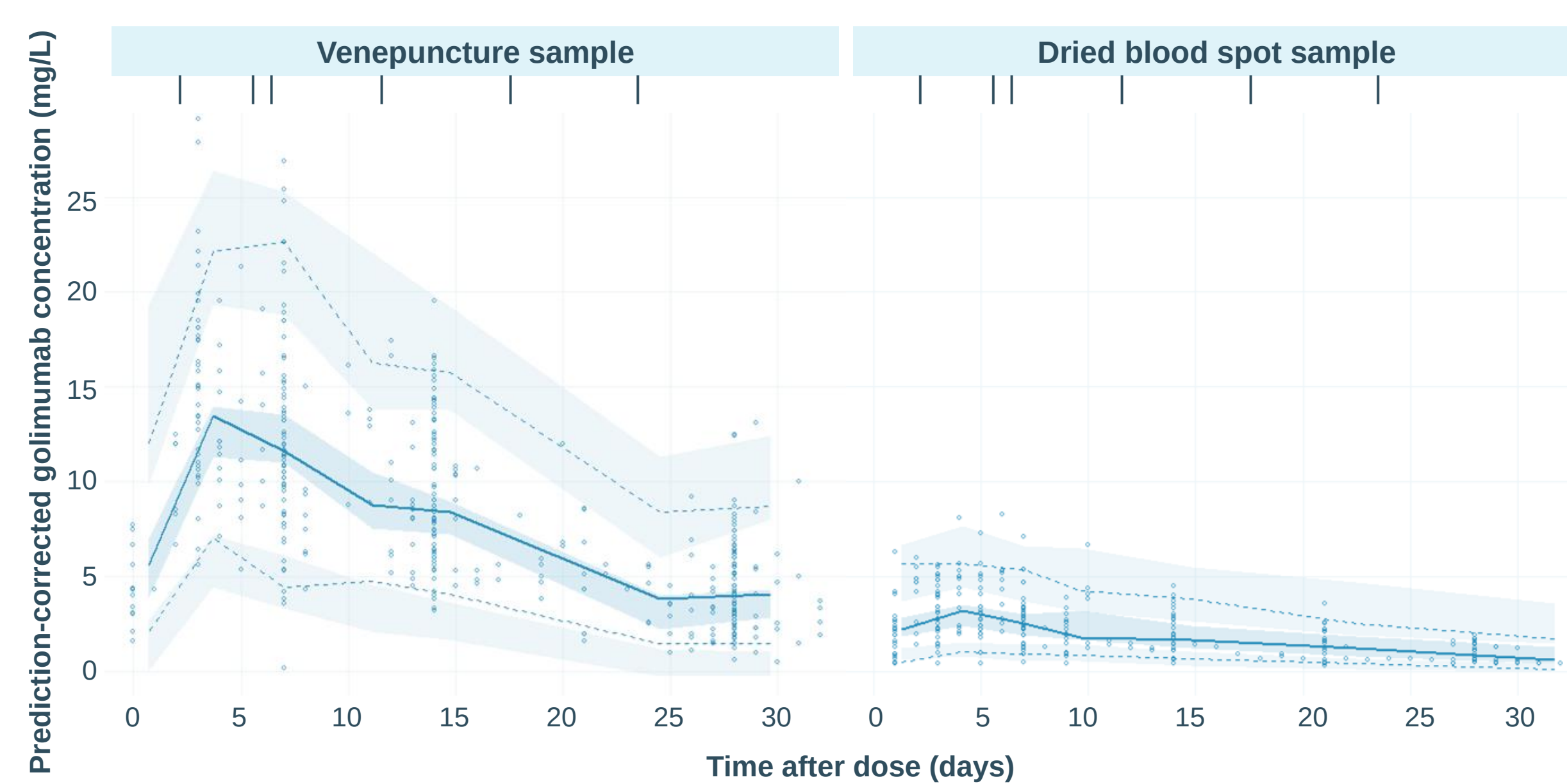


Figure 2. Prediction-corrected visual predictive check. The solid line connects the observed median prediction-corrected golimumab concentrations per bin. The dashed lines connect the 5th/95th percentile of the prediction-corrected observations. The light and dark shaded areas indicate the 90% prediction intervals of 5th/95th percentiles and the median, respectively, of the simulated data ($n = 1,000$).

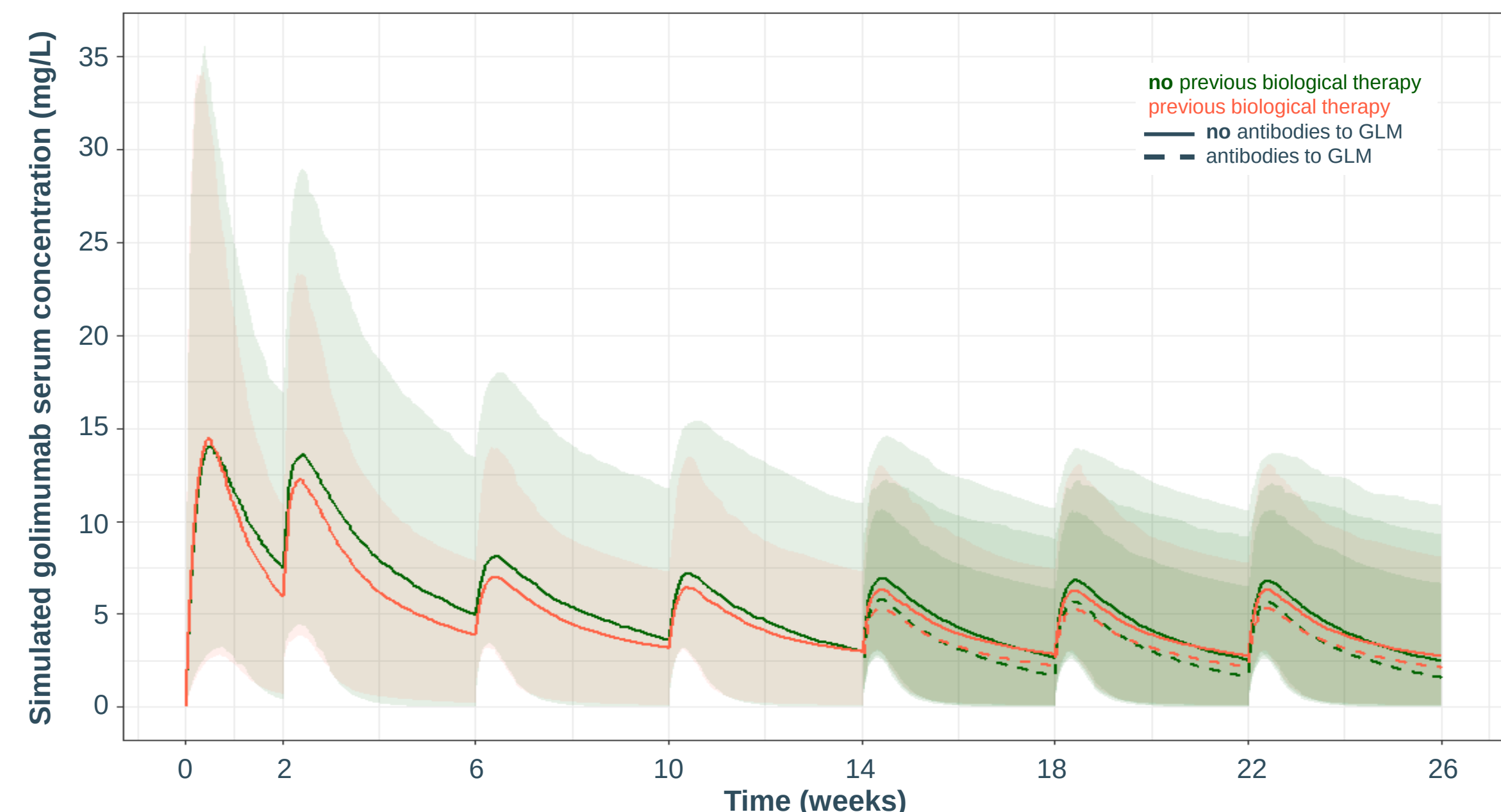


Figure 3. Simulated golimumab serum concentration-time profiles demonstrating the impact of previous biological therapy and antibodies to golimumab on the golimumab exposure following the standard induction and 100 mg maintenance dosage regimen. Data represent the median and 95% prediction interval of 1,000 simulated patients.

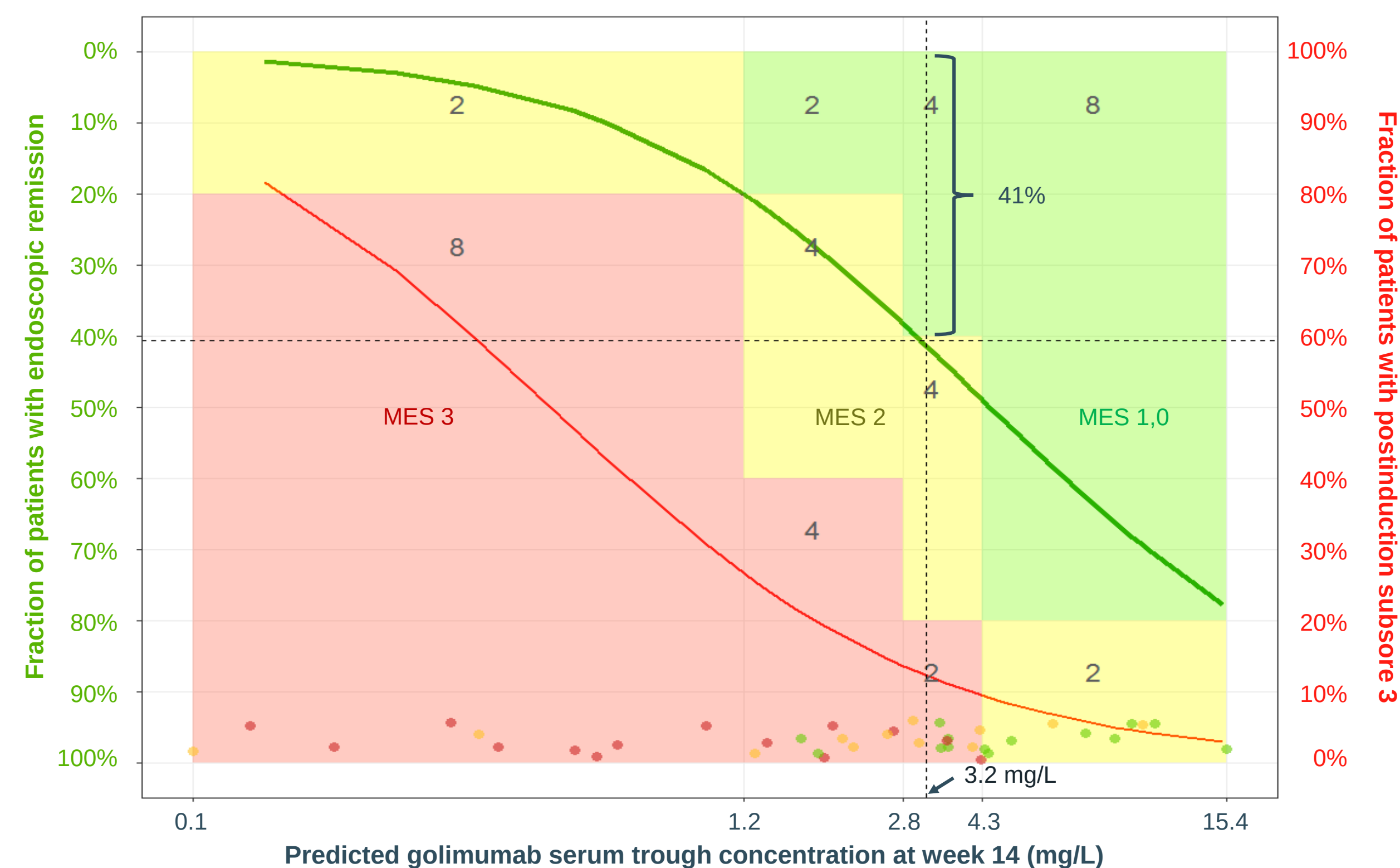


Figure 4. Goodness-of-fit of the exposure-response model. Observed (tiles) fractions of patients attaining post-induction MES 3 (red), 2 (yellow) and ≤ 1 (green) and predicted (lines) fractions of patients attaining post-induction MES 3 (red) and ≥ 1 (green) as a function of the predicted golimumab serum trough concentration at week 14 (four quantiles). Grey numbers indicate the number of patients in each bin.

References

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