

Introduction

Ustekinumab is a human IgG1 monoclonal antibody and is approved for the treatment of patients with moderate-to-severe Crohn's disease (CD). In the UNITI endoscopy sub-study, only 17.4% of patients with CD on ustekinumab achieved endoscopic response and 10.9% of patients achieved endoscopic remission at week 44 (w44).¹

Aim

To evaluate the impact of alternative ustekinumab dosage regimens on endoscopic outcomes based on a population pharmacokinetic-pharmacodynamic (popPK-PD) modeling and simulation analysis.

Methods

Real-world data were obtained from 83 patients with moderate-to-severe CD enrolled in a prospective open-label cohort study (94% biological-refractory).²

All patients received intravenous ustekinumab (~6 mg/kg), followed by every-eight-week (q8w) subcutaneous maintenance therapy (90 mg).

Endoscopic response (50% decrease in simple endoscopic score for CD [SES-CD] at w24) and endoscopic remission [SES-CD≤2] were assessed at baseline and w24 in 80 patients.

Modeling and simulation were performed using NONMEM 7.4.

Results

1. Three sequential models were developed (Figure 1).

A two-compartment population popPK model linking ustekinumab dose to ustekinumab exposure.

An indirect response popPK-PD model describing the effect of ustekinumab exposure on fecal calprotectin (fCal).

A logistic regression popPD model linking fCal to endoscopic outcomes.

2. Dose-exposure-biomarker-response relationship

Ustekinumab clearance increased with increasing bodyweight and decreasing serum albumin.

fCal decreased with increasing ustekinumab exposure.

The probability of endoscopic response (Figure 3a) and endoscopic remission (Figure 3b) increased with decreasing fCal.

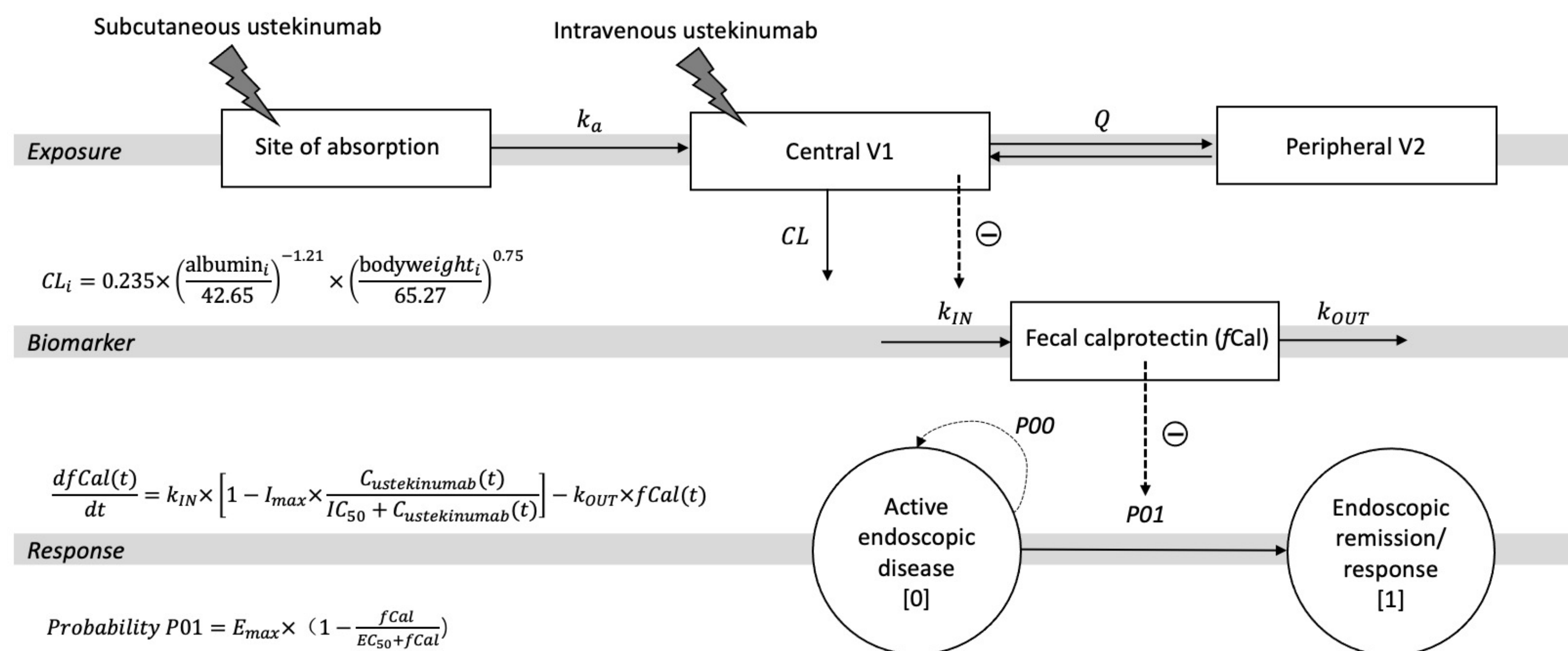


Figure 1. Schematic of the sequential models of ustekinumab in patients with CD.

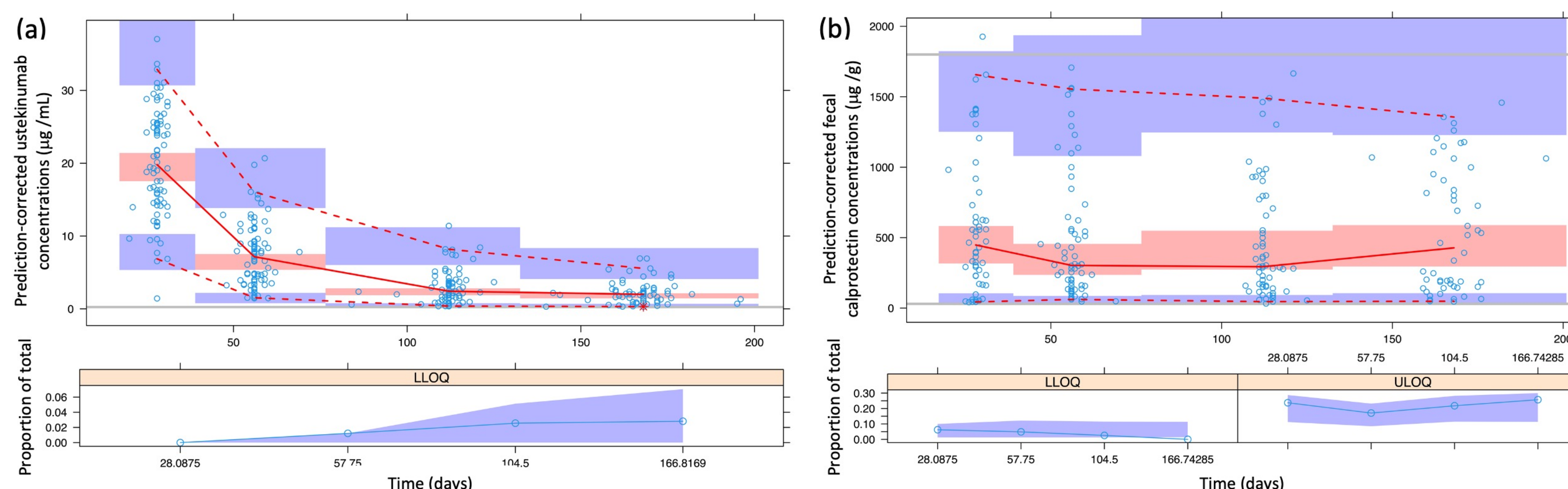


Figure 2. Visual predictive check of the popPK model (a) and the popPK-PD model (b). LLOQ: lower limit of quantification, ULOQ: upper limit of quantification.

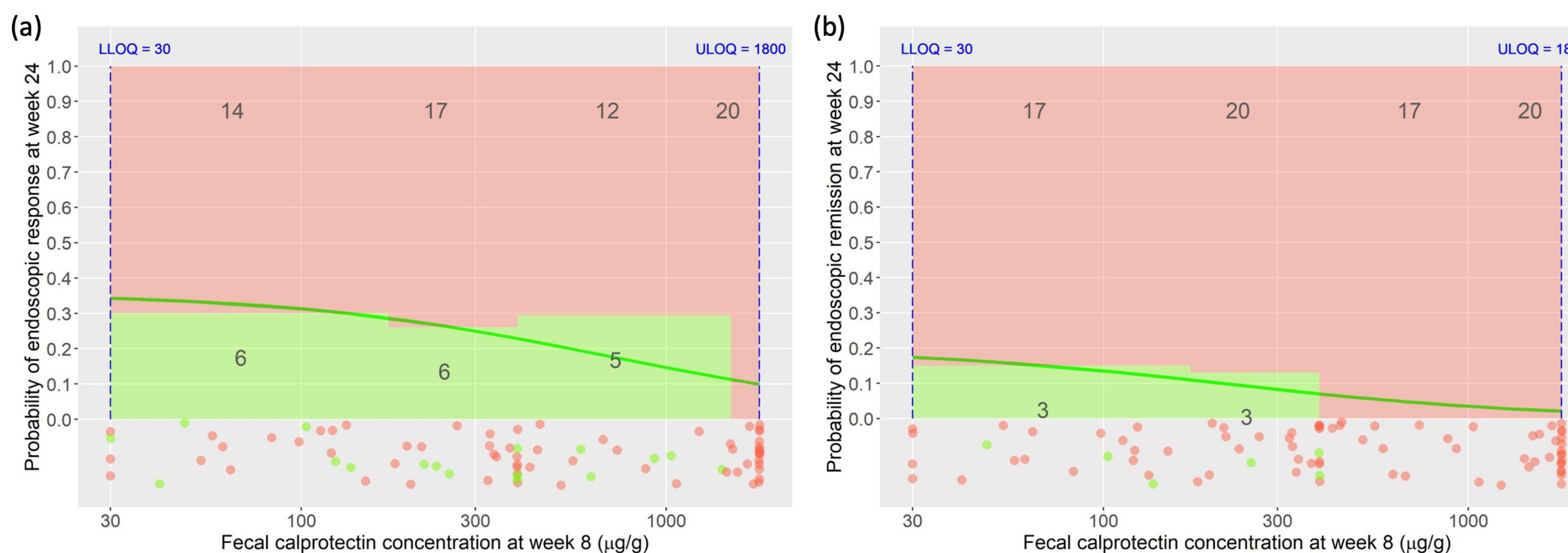


Figure 3. Goodness-of-fit plots of the outcome model. Observed (green tiles) and predicted (green line) fractions of patients achieving endoscopic response (a) or endoscopic remission (b) at w24 are presented. Red tiles represent the observed fractions of patients not attaining endoscopic outcomes. Grey numbers indicate the number of patients in each quartile of fCal concentrations. Patients achieving endoscopic outcomes (green dots) or not (red dots) at w24 are plotted.

3. Simulations

A total of 3,000 virtual patients were created.

Interval shortening from q8w to q4w maintenance dosing predicted limited gain in the proportion of patients achieving endoscopic response and remission in highly refractory patients (Table 1).

Table 1. Simulation of q4w and q8w maintenance dosing of ustekinumab

Simulated results at steady state	q4w maintenance (90 mg)	q8w maintenance (90 mg)
Median serum concentration of ustekinumab at trough	5.3 µg/mL	1.3 µg/mL
Median concentration of fCal at trough	424 µg/g	796 µg/g
Endoscopic response rate	6.7%	4.2%
Endoscopic remission rate	22.2%	16.7%

Conclusion

Based on the results from this study, we recommend an individualized, two-step monitoring approach, consisting of fCal monitoring and, only when fCal is/remains high, ustekinumab monitoring (Figure 4).

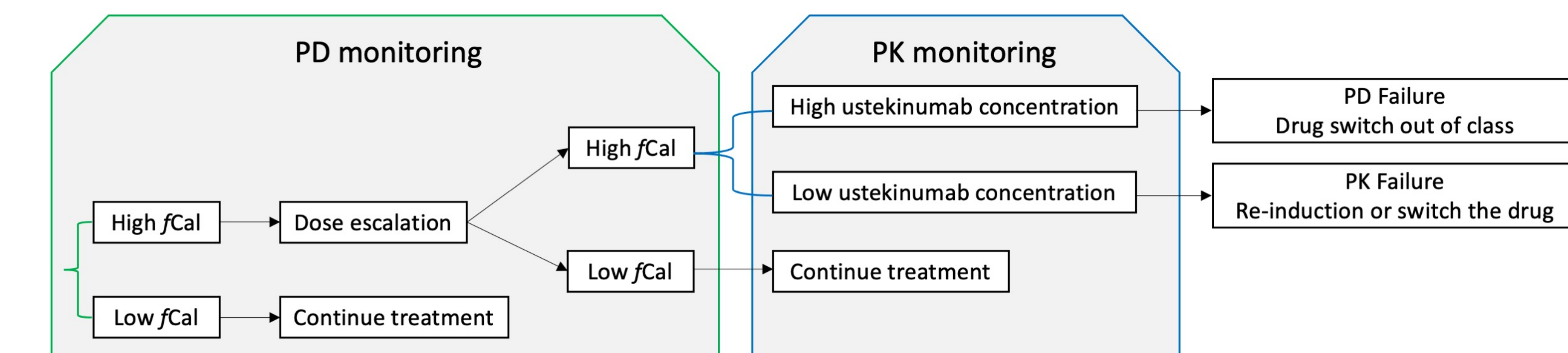


Figure 4. Recommended flowchart for therapeutic drug monitoring of ustekinumab in patients with CD. Drug switch out of class: switch to a drug with another mechanism of action.

The optimal concentration cut-offs of fCal and ustekinumab are yet to be identified based on larger studies.

Although our analyses showed that q4w dosing resulted in lower fCal concentrations, the proportion of patients achieving endoscopic remission was limited.

References

- Rutgeerts P, Gasink C, Chan D, et al. Efficacy of Ustekinumab for Inducing Endoscopic Healing in Patients With Crohn's Disease. *Gastroenterology* 2018; 155: 1045–58.
- Verstockt B, Dreesen E, Noman M, et al. Ustekinumab Exposure-outcome Analysis in Crohn's Disease Only in Part Explains Limited Endoscopic Remission Rates. *J Crohns Colitis* 2019; 13: 864–72.

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