

# Pharmacokinetic and Pharmacodynamic Modeling of Serum Etrolizumab and Circulating $\beta 7$ Receptor Occupancy in Patients With Ulcerative Colitis

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## Abstract

Etrolizumab, a humanized monoclonal antibody, specifically binds to the  $\beta 7$  subunit of the heterodimeric integrins  $\alpha 4\beta 7$  and  $\alpha E\beta 7$ . Pharmacokinetic (PK) and pharmacodynamic (PD) data were collected from an etrolizumab phase I trial in patients with moderate to severe ulcerative colitis (UC). We developed a mechanism-based model to simultaneously describe the kinetics of serum etrolizumab concentration and free  $\beta 7$  receptors on circulating intestinal-homing CD4<sup>+</sup> T lymphocytes. Included in the analysis were 38 phase I UC patients who received single or 3 monthly doses of etrolizumab intravenously or subcutaneously across a dose range of 0.3 to 10 mg/kg. A quasi-steady-state target-mediated drug disposition model was developed to describe the dynamic interaction between serum etrolizumab concentration and free  $\beta 7$  receptors on intestinal-homing CD4<sup>+</sup> T lymphocytes in UC patients. The time profiles of serum etrolizumab and absolute counts of  $\beta 7^+$  lymphocytes (expressed as percentage of baseline level) were well described by the quasi-steady-state target-mediated drug disposition model. The model was able to characterize the maximum drug occupancy of  $\beta 7$  receptors on intestinal-homing CD4<sup>+</sup> T lymphocytes and the concentration-dependent duration of occupancy. The 90% effective concentration for etrolizumab to saturate the  $\beta 7$  receptors on intestinal homing CD4<sup>+</sup> T cells was 1.3  $\mu\text{g/mL}$ . PK and PD profiles predicted by the model were consistent with observations from a subsequent phase 2 study. In conclusion, an integrated PK/PD model developed in this analysis reasonably described serum etrolizumab PK profiles and the relationship between PK and PD (free  $\beta 7$  receptors on circulating intestinal-homing CD4<sup>+</sup> T lymphocytes) in UC patients.

## Keywords

etrolizumab,  $\beta 7$  receptors, QSS TMDD model, pharmacokinetics, pharmacodynamics

Inflammatory bowel disease (IBD), a chronic inflammatory disease of the gastrointestinal tract, consists of 2 major forms: ulcerative colitis (UC) and Crohn disease. Both diseases are associated with an aberrant immune response to microbial antigens in genetically susceptible individuals in response to environmental triggers.<sup>1,2</sup> A number of new key mediators and biological pathways have been implicated in this immune dysregulation. One important pathway involves leukocyte trafficking and infiltration of lymphocytes into the submucosal tissue of the gastrointestinal tract.<sup>3</sup> Several newly approved or in-development therapies for the treatment of IBD use monoclonal antibodies (mAbs) to block the influx of proinflammatory cells into the intestinal mucosa through integrin-mediated leukocyte tethering, migration, and arrest.<sup>4</sup>

Etrolizumab is a humanized immunoglobulin G1 mAb with a dual mechanism of action that specifically targets the  $\beta 7$  subunit of both  $\alpha 4\beta 7$  and  $\alpha E\beta 7$  heterodimeric integrins. The majority of  $\beta 7$  integrin-expressing cells in the circulating intestinal-homing CD4<sup>+</sup> T lymphocytes are  $\alpha 4\beta 7$ -positive cells, whereas  $\alpha E\beta 7$ -positive cells are found primarily within mucosal

tissues in the gut on intraepithelial lymphocytes.<sup>5</sup> By binding to the  $\alpha 4\beta 7$  integrin, etrolizumab blocks the engagement of circulating lymphocytes with the mucosal addressin cell adhesion molecule 1 (MAdCAM-1) ligand and inhibits  $\alpha 4\beta 7$ /MAdCAM-1-mediated trafficking of lymphocytes from blood to the intestinal mucosa, thereby reducing the inflammation in gut tissue. In addition, etrolizumab, on binding to  $\alpha E\beta 7$  integrin,

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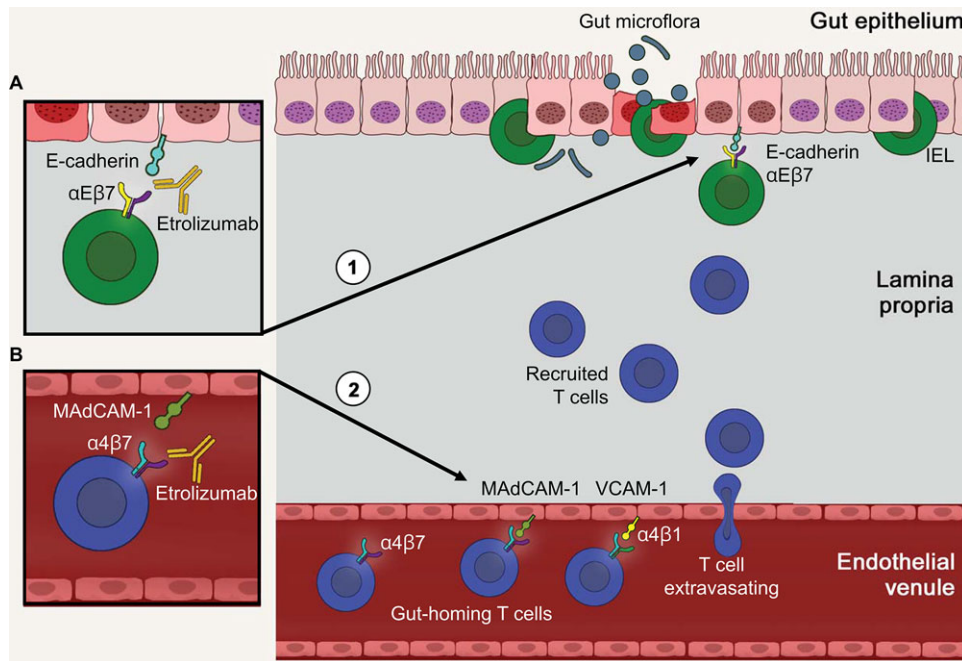
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**Figure 1.** Etrolizumab mechanism of action. Etrolizumab is a humanized IgG1 monoclonal antibody that selectively targets the  $\beta 7$  subunit of the  $\alpha 4\beta 7$  and  $\alpha E\beta 7$  integrins with high affinity and blocks interactions with their respective ligands, mucosal addressin cell adhesion molecule 1 (MAdCAM-1) and E-cadherin. IEL indicates intraepithelial lymphocytes.

prevents  $\alpha E\beta 7$ -expressing lymphocytes from interacting with the ligand E-cadherin, thereby inhibiting the retention of  $\alpha E\beta 7$  cells in the intestinal intraepithelial compartment (Figure 1).<sup>2,5</sup> This gut-selective pharmacologic mechanism avoids broad-spectrum systemic immunosuppression and has been shown to be clinically safe and effective in inducing clinical remission in patients with UC or Crohn disease.<sup>6–8</sup> Etrolizumab has been evaluated in patients with moderate to severe UC in 1 phase 1 study (ABS4262g) and 1 phase 2 study (ABS4986g, EUCALYPTUS).<sup>6,9</sup> The phase 1 study evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of etrolizumab following single or multiple doses given by intravenous (IV) or subcutaneous (SC) injections.<sup>9</sup> In the phase 2 study, clinically meaningful induction of disease remission was observed in etrolizumab-treated patients without significant safety concerns.<sup>6</sup> Therefore, etrolizumab has the therapeutic potential for treatment of IBD.

For the purpose of predicting the exposure and pharmacologic response of etrolizumab in IBD patients and facilitating dose selection for future clinical studies, population PK/PD analysis was conducted using phase 1 data to elucidate the relationship between serum etrolizumab concentration and  $\beta 7$  receptors (ie, cells with  $\beta 7$  receptors available for ligand binding) on circulating intestinal-homing CD4<sup>+</sup> T lymphocytes. Modeling the interaction between etrolizumab and its target ( $\beta 7$ -expressing cells, measured as a PD biomarker) in the blood is clinically relevant for treating a gut disease

like UC because PK/PD interactions in the blood reflect the pharmacologic effect of etrolizumab, which blocks the trafficking of gut-homing lymphocytes into the intestinal mucosa. The PK and PD of mAbs are often influenced by a complex mechanism known as target-mediated drug disposition (TMDD), which results from the high-affinity binding of mAbs to their molecular targets and the subsequent degradation of mAb-target complexes via fluid-phase or receptor-mediated endocytosis.<sup>10</sup> As a result, TMDD modeling has been commonly used to describe the dynamics of the drug-target interaction for mAbs. Full TMDD models are often overparameterized, and the characterization of all PK/PD parameters may not be feasible because of the limitation of collecting all required PK/PD data in many of the clinical study settings. Therefore, a quasi-steady-state (QSS) approximation approach requiring fewer parameters<sup>11–15</sup> was used to develop a TMDD model that fits clinical PK/PD data. This analysis aimed to simultaneously fit the kinetics of both serum etrolizumab concentration and circulating intestinal-homing CD4<sup>+</sup> T lymphocytes with free  $\beta 7$  receptors using a QSS TMDD model in order to quantify the 90% effective concentration ( $EC_{90}$ ) for  $\beta 7$  receptor drug occupancy on intestinal-homing CD4<sup>+</sup> T lymphocytes.

## Methods

Etrolizumab PK/PD data, including serum concentrations of free etrolizumab (PK) and changes in

levels of intestinal-homing CD4<sup>+</sup> T lymphocytes with free  $\beta 7$  receptors available for ligand binding (PD), were obtained from an industry-sponsored phase 1 study, registered under ClinicalTrials.gov identifier, NCT00694980. Study participants were recruited from 15 centers in Canada, the United States, and Europe (the United Kingdom, Belgium, The Netherlands, and Germany). Institutional review boards at each study site approved the protocol, and all subjects provided written informed consent.

#### Phase I Clinical Trial in Patients With Moderate to Severe UC

The design of the phase 1 trial for etrolizumab has been previously described.<sup>9</sup> Briefly, the phase 1 study was a randomized within-cohort, placebo-controlled, double-blind study involving a single-ascending-dose (SAD) stage followed by a multiple-dose (MD) stage. The trial was designed to evaluate the safety, tolerability, PK, and PD of etrolizumab in patients with moderately to severely active UC. In the SAD stage of the study, 25 patients ( $n = 5/\text{cohort}$ , 75% were male in the etrolizumab arms; randomly assigned 4:1 [etrolizumab:placebo]) were enrolled and treated with a single dose of etrolizumab at 1 of 4 IV dose levels (0.3, 1.0, 3.0, or 10 mg/kg IV), 1 dose of 3 mg/kg SC, or placebo, followed by an 18-week safety follow-up period. In the MD stage, 22 patients (72% were male in the etrolizumab arms) were randomly assigned 5:1 (except for 2 dose groups at 4:1), etrolizumab:placebo with IV or SC once every 4 weeks at 4 different dose levels. Dosing occurred at study days 1, 29, and 57 at the following doses: etrolizumab:placebo 0.5 mg/kg SC ( $n = 4:1$ ), 1.5 mg/kg SC ( $n = 5:1$ ), 3.0 mg/kg SC ( $n = 4:1$ ), or 4.0 mg/kg IV ( $n = 5:1$ ), followed by a 20-week safety follow-up period after the final doses of study drug had been administered. Except for patients who received placebo, no patients from the SAD stage of the phase 1 study were allowed to take part in the MD stage.<sup>9</sup>

In the SAD stage of the study, intensive PK serum sampling was conducted on all subjects at predose, postdose on study day 1 (1 hour postdose [IV cohorts only], and 4 hours postdose), and then on study days 2, 4, 8, 15, 22, 29, 43, 57, 71, 99, and 127 (or at early treatment termination [ET]). In the MD stage, PK serum samples were collected on study days 1 (predose, 1 hour postdose [IV cohorts only], and 4 hours following first dose), 2, 15, 29 (before second dose, 1 hour postdose [IV cohorts only], and 4 hours following second dose), 30, 43, 57 (before third dose, 1 hour postdose [IV cohorts only], and 4 hours following third dose), 58, 60, 64, 67, 71, 85, 99, 113, 141, 169, and 197 (or at ET). For antidrug antibody (ADA) assessment, serum samples were collected at study day 1 (predose) and days 15, 29,

57, 99, and 127 or ET in the SAD stage; for the MD stage, samples were collected before dosing on study days 1, 29, 57, and on study days 64, 85, 113, 141, 169, and 197 or ET. Whole-blood samples were collected to evaluate  $\beta 7$ -expressing circulating intestinal-homing CD4<sup>+</sup> T lymphocytes (named " $\beta 7^+$  cells" hereafter) following single or multiple IV or SC administrations of etrolizumab. In the SAD stage of the study, peripheral blood samples for  $\beta 7^+$  cells were obtained at screen, day 1 (predose), and study days 2, 8, 15, 22, 29, 43, 57, 71, 99, and 127 or ET. In the MD stage, peripheral blood samples were obtained at screen, day 1 (predose), study days 2, 15, 29 (before second dose), 30, 43, 57 (before third dose), as well as study days 58, 64, 71, 85, 99, 113, 141, 169, and 197 or ET.

#### Assays for Measuring Etrolizumab Serum Concentration, ADAs, and Free $\beta 7$ Receptors in Peripheral Blood

As previously reported,<sup>9</sup> free serum etrolizumab concentrations (available for binding to  $\beta 7$ -expressing cells) were measured using a validated sandwich enzyme-linked immunosorbent assay (ELISA), with a minimum quantifiable concentration of 0.0125  $\mu\text{g}/\text{mL}$ . Validation of the human PK ELISA showed both accuracy and precision to be within  $\pm 20\%$  of nominal for quality controls across the entire dynamic range of the assay. Soluble  $\alpha 4\beta 7$  has not been conclusively demonstrated in human serum. Etrolizumab PK assay validation experiments showed that 1.5  $\mu\text{g}/\text{mL}$  recombinant  $\alpha 4\beta 7$  inhibited the recovery of a very low concentration (20 ng/mL) of etrolizumab by only 34%, indicating a minimal impact by soluble  $\alpha 4\beta 7$  on the PK assay. Microtiter plates were coated with anti-etrolizumab clone 4D10 at 1.0  $\mu\text{g}/\text{mL}$  to capture etrolizumab. Biotinylated anti-etrolizumab clone 15H5 and streptavidin conjugated to horseradish peroxidase were used as detection agents. A peroxidase substrate (tetramethylbenzidine) was added to develop color, and the plates were read at 450 nm for detection absorbance and at 620 or 630 nm for reference absorbance.

A validated antibody-bridging electrochemiluminescence assay was used to determine the development of ADAs. Serum samples were first screened for the presence of ADAs. Those that tested positive for ADA were confirmed by immunodepletion. Samples with confirmed ADA responses were further diluted to obtain titer values. ADAs in serum were detected with a minimum reportable titer value of 1.30 titer units (corresponding to a minimum 1/20 sample dilution).

The absolute number of  $\beta 7^+$  cells, defined as  $\beta 7$ -expressing circulating intestinal-homing CD4<sup>+</sup> T lymphocytes (CD3<sup>+</sup>CD4<sup>+</sup>CD45RA<sup>-</sup> $\beta 7^{\text{high}}$ ), with free  $\beta 7$  receptors available for ligand binding were assessed by flow cytometry using fluorescently labeled etrolizumab that only binds to free (unbound to etrolizumab and

available for ligand binding)  $\beta 7$  receptors. Specifically, the absolute number (ABS) of intestinal-homing CD4<sup>+</sup> T lymphocytes with free  $\beta 7$  receptors were measured at each time point as  $ABS = (\text{percentage of gated population by fluorescence-activated cell sorting}) \times (\text{total lymphocyte counts by complete blood count})$  and expressed as a percentage of predose baseline ( $ABS, \%BL$ ) per given patient, thus allowing receptor normalization to the different baseline levels across all patients in the study. The actual number of  $\beta 7$  receptors expressed on each intestinal-homing CD4<sup>+</sup> T lymphocyte cannot be determined by this assay, but for the purpose of the modeling effort, we assumed that the concentration of free  $\beta 7$  receptors is directly proportional to the number of  $\beta 7^+$  cells with free  $\beta 7$  receptors. Hence, although the PD input data for the TMDD modeling were the absolute numbers of intestinal-homing CD4<sup>+</sup> T lymphocytes with free  $\beta 7$  receptors (expressed as  $ABS, \%BL$ ), the modeling process named these PD data as free circulating  $\beta 7$  receptors.

For each patient, baseline is defined as the average of the 2 predose values collected at screen and at day 1 predose. In addition to staining with fluorescein isothiocyanate-conjugated etrolizumab (for free  $\beta 7$ ), staining with a nonblocking anti- $\beta 7$  antibody (different epitope to etrolizumab) was also performed to demonstrate the extent of  $\beta 7$  expression on the cell surface before and after etrolizumab treatment.

#### PK/PD Model

A QSS TMDD model was developed to characterize the relationship between serum etrolizumab concentration and free circulating  $\beta 7$  receptors ( $ABS, \%BL$ ). The structural PK/PD model of etrolizumab is shown in Figure 2. Following SC doses of etrolizumab, the absorption of etrolizumab to the central compartment is described by a first-order absorption rate constant ( $k_a$ ). Absolute bioavailability ( $F$ ) was estimated by simultaneously analyzing SC and IV PK data. Following IV infusion or SC absorption, etrolizumab is distributed into a central compartment with a volume of distribution  $V_2$  and further distributed from a central compartment to a peripheral compartment with a volume of distribution  $V_3$ . The elimination of free etrolizumab was characterized by a linear pathway ( $CL$ ) or by binding to its target (ie,  $\beta 7$  receptors). The binding of etrolizumab with  $\beta 7$  receptors was considered reversible with association and dissociation rate constants  $k_{on}$  and  $k_{off}$ , respectively. Etrolizumab bound to the  $\beta 7$  receptor (complex) was assumed to be cleared by cellular internalization with an internalization rate constant  $k_{int}$ . The production of  $\beta 7$  receptors was assumed to follow 0-order kinetics characterized by the synthesis rate constant  $k_{syn}$ , and the degradation followed a first-order process characterized by an

elimination rate constant  $k_{deg}$ . Before drug treatment,  $\beta 7$  receptors were considered to be at steady state. Thus,  $k_{syn} = k_{deg} \times R_0$ , where  $R_0$  is the baseline concentration of free  $\beta 7$  receptors. Under the QSS approximation, the free drug, the free target ( $\beta 7$  receptors), and the drug-receptor complex were assumed to be in a QSS, and the QSS constant  $K_{ss}$  was defined as  $K_{ss} = (k_{off} + k_{int})/k_{on}$ . Free etrolizumab concentration ( $C_f$ ) was expressed through a total etrolizumab concentration ( $A_2/V_2$ ) and total  $\beta 7$  receptors concentration ( $R_{tot}$ ). The differential equations of the QSS TMDD model are shown as follows (Equation 1):

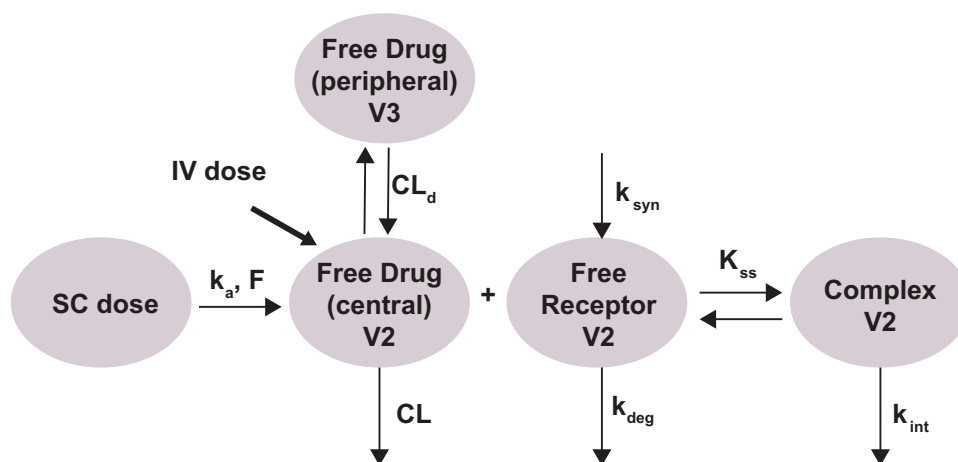
$$\begin{aligned} \frac{dA_1}{dt} &= -k_a A_1 \\ \frac{dA_2}{dt} &= k_a A_1 - (CL + CL_d) C_f + \left( \frac{CL_d}{V_3} \right) A_3 \\ &\quad - \frac{R_{tot} k_{int} C_f}{K_{ss} + C_f} V_2 \\ \frac{dA_3}{dt} &= CL_d C_f - \left( \frac{CL_d}{V_3} \right) A_3 \\ \frac{dR_{tot}}{dt} &= k_{deg} R_0 - k_{deg} R_{tot} - (k_{int} - k_{deg}) \frac{R_{tot} C_f}{K_{ss} + C_f} \\ C_f &= \frac{1}{2} \left[ \left( \frac{A_2}{V_2} - R_{tot} - K_{ss} \right) \right. \\ &\quad \left. + \sqrt{\left( \frac{A_2}{V_2} - R_{tot} - K_{ss} \right)^2 + 4K_{ss} \frac{A_2}{V_2}} \right] \end{aligned} \quad (1)$$

Initial conditions for these equations are the following:

$$A_1(0) = \text{Dose}; A_2(0) = 0; A_3(0) = 0;$$

$$R_{tot}(0) = R_0 = \frac{k_{syn}}{k_{deg}}$$

Here  $A_1$  = total drug amount in the depot compartment;  $A_2$  = total drug amount in the central compartment;  $A_3$  = free drug amount in the peripheral compartment;  $V_2$  = volume of the central compartment;  $V_3$  = volume of the peripheral compartment;  $CL$  = nonspecific clearance;  $CL_d$  = distribution clearance of free drug between the central and peripheral compartment;  $C_f$  = free drug concentration;  $k_a$  = rate of absorption;  $F$  = SC bioavailability;  $R_{tot}$  = total  $\beta 7$  receptor concentration;  $R_0$  = baseline concentration of free  $\beta 7$  receptor;  $k_{deg}$  = degradation rate of free  $\beta 7$  receptor;  $k_{syn}$  = synthesis rate of  $\beta 7$  receptor ( $k_{syn} = k_{deg} \times R_0$ );  $k_{int}$  = internalization rate for drug- $\beta 7$  receptor complex;  $K_{ss}$  = QSS constant for the  $\beta 7$  receptor.



**Figure 2.** Schema of the 2-compartment model with target-mediated drug disposition (TMDD) and quasi-steady-state (QSS) approximation of the pharmacokinetics. CL indicates non-specific clearance;  $CL_d$ , intercompartment clearance; F, bioavailability of SC dose; IV, intravenous;  $k_a$ , absorption rate constant;  $k_{deg}$ , degradation rate constant;  $k_{int}$ , complex internalization rate constant;  $K_{ss}$ , quasi-steady-state constant for the drug-receptor complex;  $k_{syn}$ , synthesis rate constant; V2, central volume; V3, peripheral volume.

Free receptor concentration R can be expressed as:

$$R = \frac{R_{tot}K_{ss}}{K_{ss} + C_f}$$

To derive equations for the PD measurements ( $R_f$  [ABS, %BL]), it was assumed that the number of cells expressing  $\beta 7$  receptors (ABS) detected by the assay is directly proportional (with the coefficient  $\gamma$ ) to the free  $\beta 7$  receptor concentration (R). Then,

$$ABS(0) = \gamma R_0;$$

$$ABS(t) = \gamma R(t) = \gamma \frac{R_{tot}K_{ss}}{K_{ss} + C_f};$$

$$R_f (\%BL) = 100 \times \frac{ABS(t)}{ABS(0)} = 100 \times \frac{R_{tot}K_{ss}}{K_{ss} + C_f} \frac{1}{R_0}$$

where  $R_f$  (ABS, %BL) is the number of cells with free  $\beta 7$  receptor expressed as a percentage of a baseline number of these cells.

Models with  $E_{max}$  and a sigmoid function relation between absolute number of  $\beta 7$ -expressing cells (ABS) and free receptor concentration (R) were also tested but resulted in similar fits.

#### Statistical Model

The interindividual variabilities for CL,  $V_2$ , and  $k_{int}$  were described by the log-normal distributions. Residual (intra-individual) variability was described by a proportional error model for etrolizumab concentrations and a combined proportional and additive error model for  $R_f$  (ABS, %BL).

#### PK/PD Analysis

Included in the PK/PD model development were 609 data points for serum etrolizumab concentrations

and 448 data points for free circulating  $\beta 7$  receptors from 38 etrolizumab-treated UC patients in the phase 1 study.

This PK/PD modeling was performed using the non-linear mixed-effects model implemented in NONMEM 7.2 (ICON Development Solutions, Ellicott City, Maryland). The first-order conditional estimation method with interaction and ADVAN13 PREDPP subroutine was employed for all model runs. The software R-3.2.2 (R Foundation, Vienna, Austria) was used for data-set assembly, statistical computations, and graphics.

#### Model Evaluation

The adequacy of fitting was examined by the basic goodness-of-fit diagnostics, including plots of population study prediction and individual study prediction vs individual observations and distributions of individual estimates of random effects.

For the final model, a visual predictive check was performed to evaluate whether the estimated fixed-effect parameters adequately described the data. Specifically, 500 Monte Carlo simulation replicates of the original phase 1 data set at each dose level were generated using the final model. Original observations at different dose levels were plotted vs time and overlaid with the summary statistics computed from the simulated data with 5th, 50th, and 95th percentiles.

To assess the precision of the parameter estimates, the final model was fitted to 1000 replicates of the data set obtained by bootstrapping the original data set. The median value of the bootstrapped parameters and their 2.5th and 97.5th percentiles were compared with the point estimates and the corresponding confidence interval obtained from the final model.

### Estimation of EC<sub>90</sub> or EC<sub>99</sub> Values for 90% or 99% Occupancy of $\beta 7$ Receptors on Circulating Intestinal-Homing CD4<sup>+</sup> T Lymphocytes

Monte Carlo simulations for a certain dose regimen were conducted for 500 replicates using the final QSS TMDD model to generate a serial data set containing free serum etrolizumab concentrations and free circulating  $\beta 7$  receptors (ABS, %BL) at matched time points. The simulated data set was used to create the profile of free circulating  $\beta 7$  receptors (ABS, %BL) vs free serum etrolizumab concentration. The drug concentrations for reaching 90% and 99% (relative to the baseline level) occupancy of the  $\beta 7$  receptors on circulating intestinal-homing CD4<sup>+</sup> T lymphocytes were then estimated based on the profile of free circulating  $\beta 7$  receptors (ABS, %BL) vs free serum etrolizumab concentrations.

### Prediction of PK/PD Profiles for the Phase 2 Study

The final QSS TMDD model was used to simulate the PK and PD profiles of etrolizumab simultaneously for the dose regimens evaluated in the phase 2 study (ClinicalTrials.gov identifier, NCT01336465). In the phase 2 study of etrolizumab, patients with moderately to severely active UC received SC etrolizumab at 1 of the following 2 dose regimens: (1) 100 mg at weeks 0, 4, and 8 (100 mg group, N = 40); or (2) 420 mg at week 0, followed by 300 mg at weeks 2, 4, and 8 (300 mg + loading dose [LD] group, N = 41). Serum samples for determining the etrolizumab exposures were obtained from all patients at predose and postdose on days 4, 14, 28, 42, 56, 60, 70, 84, 112, 140, and 196. Peripheral blood samples for free circulating  $\beta 7$  receptors were collected at screen, day 1 (predose), and postdose on days 4, 28, 42, 60, 70, 112, and 196. The model-simulated time courses for etrolizumab serum concentration and free circulating  $\beta 7$  receptors (ABS, %BL) at the median, 5th, and 95th percentiles were constructed and overlaid with the observed PK/PD data for each dose regimen group.

## Results

### Observed PK and PD Profiles in Patients With UC From Phase I Study

The PK profile of etrolizumab is generally linear and dose proportional with regard to maximum concentration and area under the curve (SAD cohorts) or area under the curve during the last dosing interval (MD cohorts) within the dose range tested.<sup>9</sup> A slight trend of nonlinearity was observed at doses  $\leq 1.0$  mg/kg (Figure 3), possibly related to target-mediated clearance at lower etrolizumab serum concentrations.<sup>9</sup> The slight nonlinearity of PK at doses  $\leq 1.0$  mg/kg resulted in shorter half-lives at lower doses (4.8 to 7.4 days at 0.3 to 1 mg/kg) compared with longer half-lives at higher doses (10.6 to 13.1 days at 3 to 10 mg/kg).

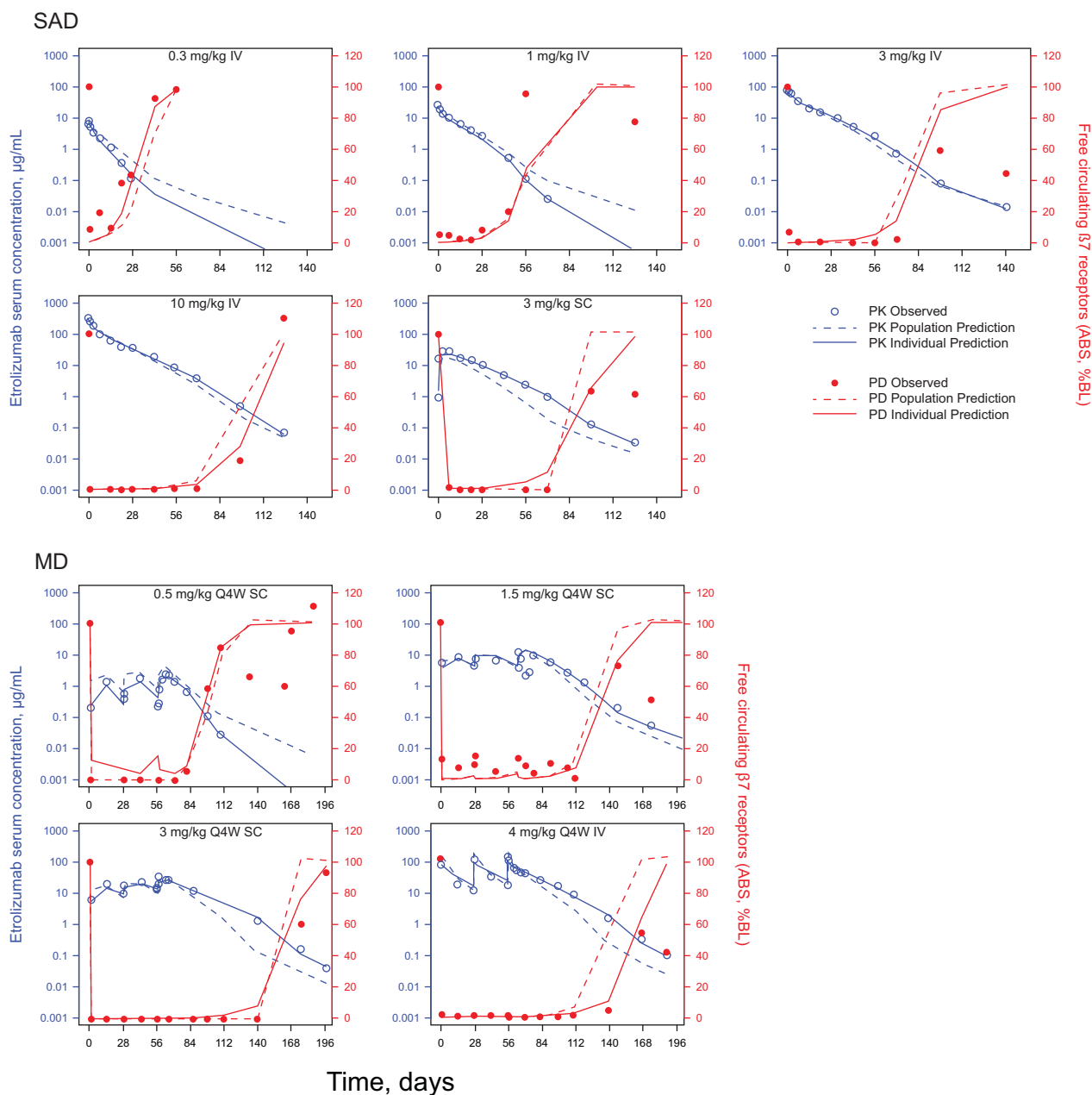
Anti-etrolizumab antibodies were detected in 2 of a total of 38 drug-treated patients. In these 2 ADA-positive patients, the ADA titer levels were low and close to the minimum reportable level (1.3 titer unit). Neither patients with detectable ADAs had any symptoms of allergic reaction or differences in their PK profiles compared with patients without ADAs.

Complete or near-complete occupancy of the  $\beta 7$  integrin on intestinal-homing CD4<sup>+</sup> T-cell subsets (indicated by nearly no detectable free  $\beta 7$  receptors) was observed at all dose levels following SC or IV administration of etrolizumab. There was an observed dose-dependent trend in the duration of complete  $\beta 7$  receptor occupancy in etrolizumab-treated patients. In cohorts that received single doses of 0.3, 1.0, and 10 mg/kg IV, cohort mean duration of complete  $\beta 7$  receptor occupancy was approximately 2, 6, or 10 weeks, respectively. In cohorts that received multiple SC doses of 0.5 mg/kg or 1.5 mg/kg etrolizumab, cohort mean duration of complete  $\beta 7$  receptor occupancy was maintained for approximately 2 to 4 weeks after administration of the final dose. In cohorts that received 3 mg/kg SC or 4 mg/kg IV of etrolizumab, the average duration of complete  $\beta 7$  receptor occupancy observed was 8 to 12 weeks after administration of the final dose. The recovery of free  $\beta 7$  receptors on intestinal-homing CD4<sup>+</sup> T lymphocytes was associated with the decrease in serum drug concentration, and a minimum serum etrolizumab concentration of 1 to 3  $\mu\text{g/mL}$  appeared to be necessary to maintain complete drug occupancy of  $\beta 7$  receptors on the intestinal-homing CD4<sup>+</sup> T lymphocytes.<sup>9</sup>

### PK/PD Model Parameters

As shown in Figure 3, the fitted time courses for both etrolizumab serum concentration and free circulating  $\beta 7$  receptors (ABS, %BL), derived from the QSS TMDD model, were in good agreement with the observed data for representative patients from different dose levels in the phase 1 study.

The PK and PD parameters estimated from the QSS TMDD model are summarized in Table 1. The parameters for serum etrolizumab concentration and free circulating  $\beta 7$  receptors (ABS, %BL) were estimated with reasonable precision. The relative standard error values of all estimations were below 20%. The model-estimated population mean values of clearance (0.303 L/day) and central volume of distribution (2.57 L) are similar to other human IgG1 mAbs in the linear dose range, and the estimated population means of the SC bioavailability (50.4%) and  $k_a$  (0.248/day) are also within the range of the population mean values of other reported mAbs.<sup>16</sup> For free circulating  $\beta 7$  receptors, the model-estimated degradation rate constant ( $k_{\text{deg}}$ ) was 0.144/day, and the synthesis rate



**Figure 3.** Comparison between observed and model-fitted etrolizumab pharmacokinetic (blue) and pharmacodynamic (red) profiles of representative patients from each cohort in etrolizumab phase I study. IV indicates intravenous; MD, multiple dose; Q4W, every 4 weeks; SAD, single ascending dose; SC, subcutaneous.

( $k_{\text{syn}} = k_{\text{deg}} \times R_0$ ) was 0.472 nM/day. The internalization rate for drug- $\beta 7$  receptor complex was estimated to be 0.0314/day, about one third of the elimination rate constant of free drug ( $CL/V_2 = 0.118/\text{day}$ ). The value for the QSS constant  $K_{\text{ss}}$  was estimated to be 0.240 nM.

Moderately high interindividual variability was estimated for  $CL$  (61.7%),  $V_2$  (57.9%), and  $k_{\text{int}}$  (87.2%). Low  $\epsilon$ -shrinkage (9%) and low  $\eta$ -shrinkage ( $\leq 30\%$ ) suggest that the model was not overparameterized, the data were sufficient to estimate all individual model parameters, and the model diagnostics were reliable.

#### Model Diagnostics

Multiple approaches of model diagnostics suggested that the model adequately described the time profiles of serum etrolizumab concentration and free circulating  $\beta 7$  receptor (ABS, %BL) after both single and multiple doses in patients with UC. Goodness-of-fit plots indicated good agreement between population or individual predicted concentration and observed concentration as well as the random distribution of conditional-weighted residuals (Figure 4). The visual predictive check shows that the simulated population serum

**Table 1.** Etrolizumab PK and PD Parameter Estimates From the Final TMDD Model With QSS Approximation in UC Patients

| Parameter                | Explanation                                     | Point Estimate (%RSE) | Bootstrap Median (2.5th, 97.5th Percentiles) |
|--------------------------|---|-----------------------|--|
| CL, mL/d                 | Nonspecific clearance                           | 303 (10.9)            | 291 (229, 374)                               |
| V <sub>2</sub> , mL      | Central volume                                  | 2570 (8.79)           | 3165 (2346, 4098)                            |
| CL <sub>d</sub> , mL/d   | Intercompartment clearance                      | 543 (12.6)            | 519 (284, 779)                               |
| V <sub>3</sub> , mL      | Peripheral volume                               | 2080 (4.78)           | 1930 (1283, 2595)                            |
| F                        | SC bioavailability                              | 0.504 (15.0)          | 0.460 (0.118, 0.754)                         |
| K <sub>a</sub> , 1/d     | Absorption rate constant                        | 0.248 (6.25)          | 0.228 (0.151, 0.321)                         |
| K <sub>ss</sub> , nmol/L | QSS constant                                    | 0.240 (7.38)          | 0.251 (0.133, 0.500)                         |
| K <sub>deg</sub> , 1/d   | Degradation rate constant                       | 0.144 (11.5)          | 0.142 (0.072, 0.205)                         |
| K <sub>int</sub> , 1/d   | Complex internalization rate constant           | 0.0314 (5.38)         | 0.0325 (0.0209, 0.0544)                      |
| R <sub>0</sub> , nmol/L  | Baseline free $\beta 7$ receptor concentration  | 3.28 (5.61)           | 3.19 (1.75, 6.97)                            |
| $\omega_{CL}$ , %        | Interindividual variability on CL               | 61.7 (8.83)           | 49.1 (29.6, 73.9)                            |
| $\omega_{V_2}$ , %       | Interindividual variability on V <sub>2</sub>   | 57.9 (4.46)           | 51.1 (32.1, 68.7)                            |
| $\omega_{K_{int}}$ , %   | Interindividual variability on K <sub>int</sub> | 87.2 (13.0)           | 69.6 (35.4, 109)                             |
| $\sigma_{prop,PK}$ , %   | PK proportional residual error                  | 27.1 (2.17)           | 26.3 (21.4, 31.0)                            |
| $\sigma_{prop,PD}$ , %   | PD proportional residual error                  | 78.2 (10.5)           | 74.5 (49.2, 126)                             |
| $\sigma_{add,PD}$        | PD additive residual error                      | 8.78 (5.73)           | 8.36 (3.66, 16.6)                            |

CL indicates clearance; CL<sub>d</sub>, intercompartment clearance; K<sub>int</sub>, internalization rate constant; PD, pharmacodynamic; PK, pharmacokinetic; QSS, quasi-steady-state; RSE, relative standard error; SC, subcutaneous; TMDD, target-mediated drug disposition; UC, ulcerative colitis; V<sub>2</sub>, central volume; V<sub>3</sub>, peripheral volume.

etrolizumab concentration and the profile of free circulating  $\beta 7$  receptors (ABS, %BL) describe the observed data reasonably well (Figure 5), indicating that the final QSS TMDD model captured the variability of data and described the time course of etrolizumab concentrations and free circulating  $\beta 7$  receptors (ABS, %BL) adequately. Bootstrapping successfully converged in 893 runs from a total of 1000 runs. As summarized in Table 1, the point estimate of model parameters all fell within the 2.5th and 97.5th percentiles of the respective values generated by bootstrapping and were very close to the median, suggesting sufficient predictive performance of the model.

**Estimated EC<sub>90</sub>/EC<sub>99</sub> Values for 90% or 99% Occupancy of  $\beta 7$  Receptors on Intestinal-Homing CD4<sup>+</sup> T Lymphocytes** Based on the simulated PK/PD data, the relationship of serum etrolizumab concentration and free circulating  $\beta 7$  receptors (ABS, %BL) was constructed, and the curve representing the median values (90%CI) is presented in Figure 6. The median (90%CI) values of EC<sub>90</sub> and EC<sub>99</sub> for etrolizumab occupying 90% or 99% (relative to the baseline level) of the peripheral  $\beta 7$  receptors were estimated to be 1.3 (0.5, 2.9)  $\mu\text{g}/\text{mL}$  and 10.1 (5.3, 16.8)  $\mu\text{g}/\text{mL}$ , respectively.

#### Model Prediction of PK/PD Profiles for Dose Regimens Evaluated in Phase 2

Figure 7 presents the model-predicted median and 5th to 95th percentile of the time profiles for serum etrolizumab concentration and free circulating  $\beta 7$  receptors (ABS, %BL) at both dose regimens evaluated in the phase 2 study (100 mg group and 300 mg + LD group). The observed PK/PD data were graphically compared with the model predictions. As shown in

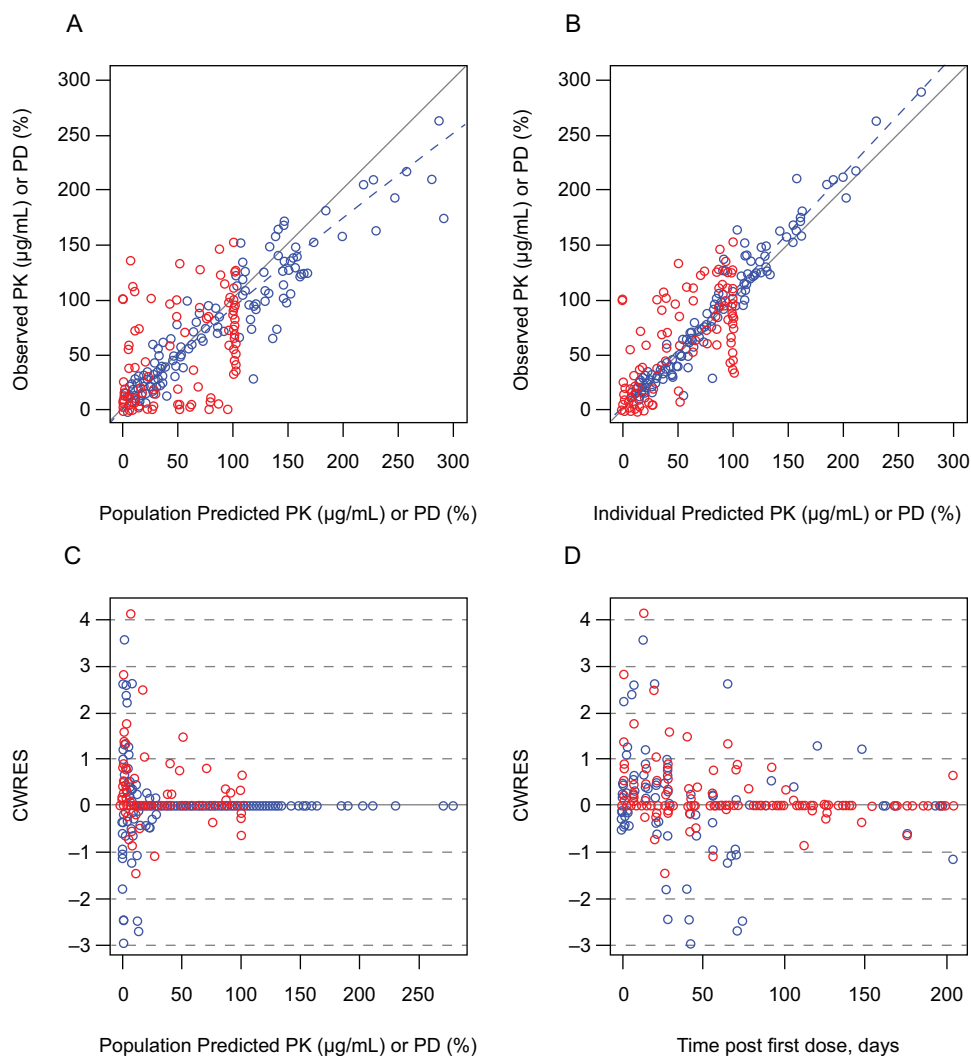
Figure 7, despite the large variability of free circulating  $\beta 7$  receptors (ABS, %BL) in the recovery phase, most observed individual data were contained within the model-predicted 90% confidence intervals. The model-predicted median values captured the trend of the observed serum etrolizumab concentration and free circulating  $\beta 7$  receptors' (ABS, %BL) time profiles appropriately.

## Discussion

Results from this study demonstrate that the QSS TMDD model reasonably describes the concentration-time profiles of both serum etrolizumab concentration and free circulating  $\beta 7$  receptors (ABS, %BL) after single- or multiple-dose administrations of etrolizumab via either IV or SC routes of administration in patients with moderately to severely active UC. The model integrated the kinetics of both etrolizumab and its target, the  $\beta 7$  subunit of the heterodimeric  $\alpha 4\beta 7$  integrin, in a mechanistic approach and estimated the PK (serum etrolizumab concentration) and PD (free circulating  $\beta 7$  receptor [ABS, %BL]) parameters with reasonable precision.

The flow cytometry assay used in our PD assessment specifically detects cells with free  $\beta 7$  receptors (defined as those receptors available for ligand binding). By use of fluorescently conjugated etrolizumab, cells with free  $\beta 7$  receptors were captured and expressed as a percentage of predose baseline level for each patient. The assay, however, is unable to determine the specific number of free  $\beta 7$  receptors on the cell surface. Instead, the percentage of cells with free  $\beta 7$  receptors was reported during data acquisition. In the presence of saturating concentrations of etrolizumab, the number



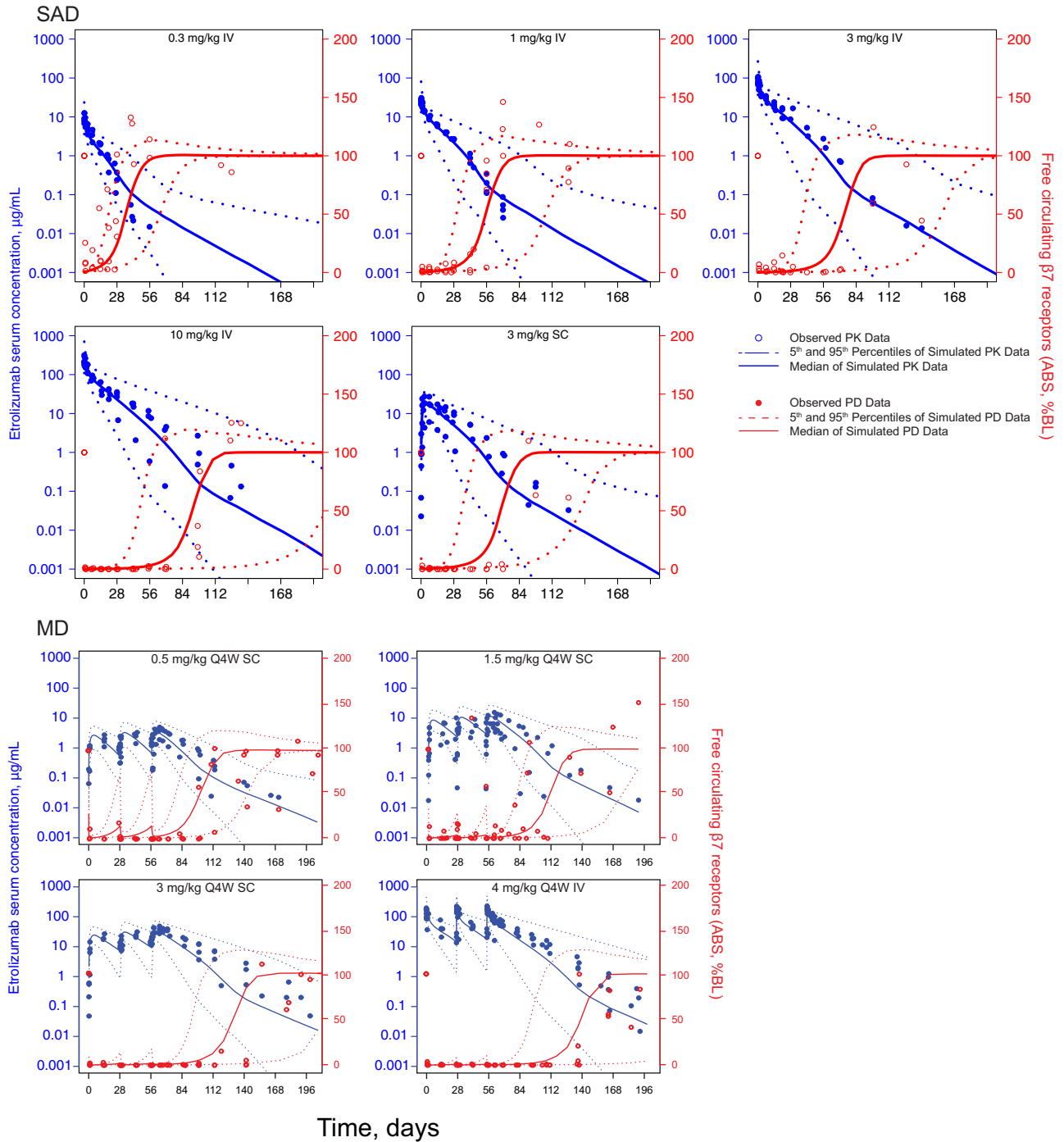


**Figure 4.** Goodness-of-fit diagnostic plots for the 2-compartment target-mediated drug disposition and quasi-steady-state model: (A) observed vs population predictions; (B) observed vs individual Bayesian predictions; (C) conditional weighted residuals (CWRES) vs population predictions; (D) conditional weighted residuals (CWRES) vs time after first dose. Blue circles and red circles represent pharmacokinetics for etrolizumab and pharmacodynamics for free circulating  $\beta 7$  receptors (ABS, BL%), respectively.

of cells with free  $\beta 7$  receptors was reduced to 0, confirming complete  $\beta 7$  receptor occupancy. When serum etrolizumab concentration decreased to below saturating level, loss of the complete  $\beta 7$  receptor occupancy led to a portion of  $\beta 7^+$  cells with free  $\beta 7$  receptors being detectable by the assay. To ensure that the reduction of detectable free  $\beta 7$  receptors is not due to  $\beta 7$  expression downregulation after etrolizumab treatment, we used a noncompeting anti- $\beta 7$  antibody capable of binding to  $\beta 7$  in the presence of etrolizumab to monitor  $\beta 7$  expression level over time. Our flow cytometry data showed that both the total number of  $\beta 7$ -expressing lymphocytes and the level of  $\beta 7$  expression remained unchanged after etrolizumab treatment. This finding supports our assumption that the number of cells expressing  $\beta 7$  receptors (ABS) being detected by the

assay is directly proportional to the free  $\beta 7$  receptor concentration.

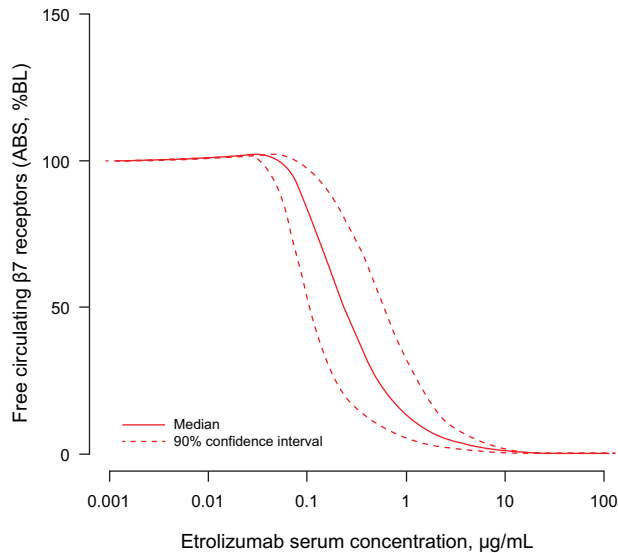
Modeling results suggest that free circulating  $\beta 7$  receptors (ABS, %BL) have a relatively small effect on etrolizumab PK. The QSS TMDD model estimated CL of etrolizumab to be 303 mL/day. Compared with a CL value of 245 mL/day estimated by a linear, 2-compartment PK-only model,<sup>17</sup> this CL value generated by the QSS TMDD PK/PD model is in good agreement. The central volume of distribution  $V_2$  is also similar whether derived from the QSS TMDD model (2570 mL) or the linear PK model (3200 mL). In fact, the observed PK profiles of etrolizumab are generally linear at most of the dose levels tested (1.5 to 10 mg/kg) except for a slight trend of nonlinearity at doses  $\leq 1.0$  mg/kg.<sup>9</sup> This suggests that target-mediated



**Figure 5.** Visual predictive check: etrolizumab original pharmacokinetic (blue dots) and pharmacodynamic (red circles) observations at different doses vs the population pharmacokinetic/pharmacodynamic model simulated data. IV indicates intravenous; MD, multiple dose; PD, pharmacodynamic; PK, pharmacokinetic; Q4W, every 4 weeks; SAD, single ascending dose; SC, subcutaneous.

clearance occurs at lower etrolizumab serum concentrations ( $<1 \mu\text{g/mL}$ ) and that free  $\beta 7$  receptors can be fully occupied (resulting in no free circulating  $\beta 7$  receptors [ABS, %BL]) when etrolizumab doses are  $>1.0 \text{ mg/kg}$ . Because the majority of the PK/PD data in the phase 1 study came from dose levels in the range of 1.5 to 10 mg/kg, it is expected that the impact of drug- $\beta 7$

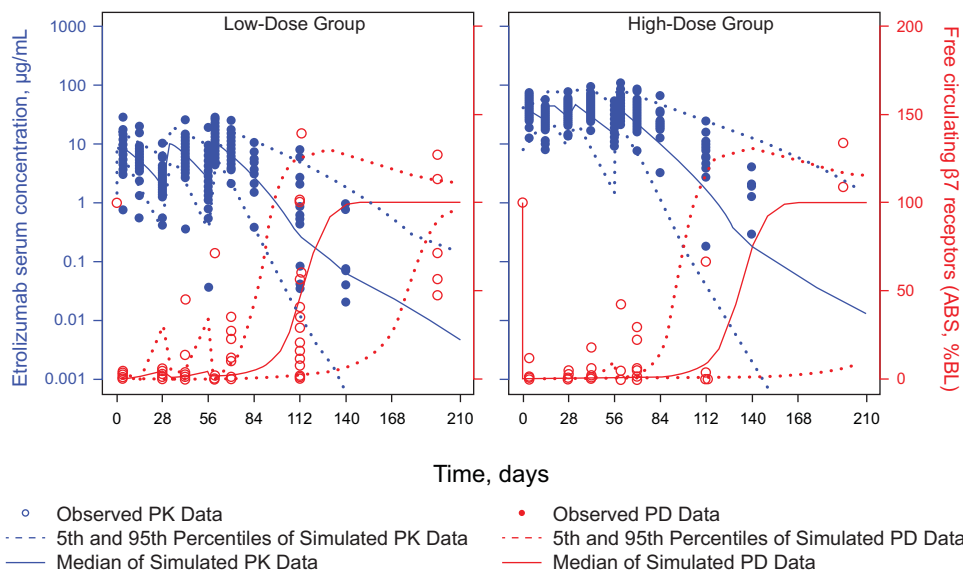
receptor interaction on etrolizumab PK is negligible in this analysis. Moreover, the therapeutic dose levels of etrolizumab are anticipated to be  $>1.0 \text{ mg/kg}$  (as tested and confirmed by the phase 2 study); therefore, a 2-compartment model with linear elimination can reasonably characterize the etrolizumab PK profile at therapeutic dose levels.



**Figure 6.** Simulated median profile of free circulating  $\beta 7$  receptors (ABS, %BL) vs etrolizumab serum concentrations (median with 90% confidence interval).

The developed QSS TMDD model is capable of characterizing the fast onset of maximum etrolizumab occupancy on  $\beta 7$  receptors and the concentration-dependent duration of receptor occupancy. Because the occupancy of  $\beta 7$  receptors occurred rapidly after dosing, and the complete or nearly complete receptor occupancy was maintained during the entire dosing period,<sup>9</sup> dynamic interactions between etrolizumab and its target, the  $\beta 7$  receptor, can only be characterized from the recovery phase with the emergence of free circulating  $\beta 7$  receptors following the discontinuation of

etrolizumab dosing. Therefore, it is preferable to collect intensive data points in the free  $\beta 7$  receptor-recovery phase during drug washout for accurate estimations of PD parameters, such as  $K_{ss}$  and  $k_{int}$ . As shown in Figure 5, our model was able to describe the time profiles of the PD-recovery phase when  $\beta 7$  receptors dissociated from the drug-target complex and recovered toward baseline following the last dose of etrolizumab. However, substantial interindividual variability was observed in the PK terminal and PD recovery phase. This could be attributed to the lack of sufficient observed data points to allow full characterization of the PK/PD profiles within the terminal phase. The model-estimated value of the QSS constant  $K_{ss}$  (0.240 nM) is higher than the drug-target binding affinity ( $K_d$ ) for  $\alpha 4\beta 7$  (0.116 nM) but lower than the  $K_d$  for  $\alpha E\beta 7$  (1.8 nM) (both  $K_d$  values were determined by equilibrium binding analysis of transfected 293 cells [Genentech, data on file]). Because  $\alpha 4\beta 7$  is expressed on the circulating intestinal-homing  $CD4^+$  T lymphocytes and  $\alpha E\beta 7$ -positive cells are found primarily within mucosal tissues in the gut on intraepithelial lymphocytes, the estimated  $K_{ss}$  from this model is thought to be more relevant to the  $K_d$  for  $\alpha 4\beta 7$ . Under the assumption of QSS approximation, the  $K_{ss}$  is expressed as the sum of  $K_d$  and  $k_{int}/k_{on}$ . Therefore, the estimated  $K_{ss}$  is usually higher than  $K_d$ .<sup>12,18</sup> The model-estimated internalization rate ( $k_{int}$ ) of the etrolizumab- $\beta 7$  receptor complex is 0.0314/day (half-life of 22 days), which is much slower than the model-estimated degradation rate ( $k_{deg}$ ) of circulating  $\beta 7$  integrins (0.144/day, half-life of 4.8 days). This means that the internalization of



**Figure 7.** Model verification. Model-predicted pharmacokinetic (PK; blue)/pharmacodynamic (PD; red) profiles for etrolizumab are generally in good agreement with the observed data for dose regimens evaluated in the phase 2 study: Left panel: etrolizumab 100 mg at weeks 0, 4, and 8; Right panel: etrolizumab 420 mg at week 0, followed by 300 mg at weeks 2, 4, and 8.

the etrolizumab- $\beta 7$  receptor complex does not have a major influence on the dynamic equilibrium of the synthesis and degradation of  $\beta 7$  receptors. Furthermore, results from flow cytometry assay showed that the expression of  $\beta 7$  receptors on intestinal-homing CD4<sup>+</sup> T lymphocytes remained unchanged after dosing with etrolizumab.<sup>6</sup> This is an important observation to support current model assumptions that the number of  $\beta 7$  receptors is constant over time and that the observed decrease in free  $\beta 7$  signal is not due to a decrease in receptor expression postdose, but rather is the result of  $\beta 7$  receptor occupancy by etrolizumab.

Based on our QSS TMDD model for etrolizumab, the median value of EC<sub>90</sub> for etrolizumab to occupy 90% of peripheral  $\beta 7$  receptors was estimated to be 1.3  $\mu\text{g/mL}$ . This is consistent with the observed PK/PD relationship from phase 1 in both single- and multiple-dose cohorts in which a minimum serum concentration range of 1 to 3  $\mu\text{g/mL}$  of etrolizumab maintained full occupancy of  $\beta 7$  receptors on the intestinal-homing, circulating CD4<sup>+</sup> T lymphocytes. In addition, results from the phase 2 study showed that full occupancy of  $\alpha 4\beta 7$  and  $\alpha E\beta 7$  T lymphocytes in colonic tissues was also observed when serum etrolizumab level was 1.7  $\mu\text{g/mL}$  or higher.<sup>6</sup> Given the similar threshold serum concentration levels of etrolizumab for saturating the free  $\beta 7$  receptors in the peripheral blood and colonic tissues, it appears that  $\beta 7$  receptor occupancy in colonic tissue correlates with that in the peripheral blood. Therefore, the occupancy of the circulating receptors in the blood can be used as a surrogate to assess receptor occupancy for the  $\beta 7$ -expressing cells in the colonic tissue in UC patients. This offers great clinical utility, as free  $\beta 7$  receptors on the circulating lymphocytes are comparatively easier to access than  $\beta 7$  cells in gut tissue; thus, the EC<sub>90</sub> value derived from the QSS TMDD model is also a good predictor for receptor occupancy in the colonic tissue.

The final QSS TMDD model derived using the phase 1 data was further verified using the observed PK/PD data from the etrolizumab phase 2 study. A good agreement between the model-predicted phase 2 PK/PD profiles and the phase 2 observed PK/PD data confirms the robustness of the model. Simulations with the QSS TMDD model-predicting PK/PD profiles in 500 patients showed that etrolizumab steady-state trough concentrations can be achieved at levels greater than or equal to EC<sub>90</sub> (1.3  $\mu\text{g/mL}$ ) in 78% or 92% of patients following etrolizumab administration of 100 mg or 300 mg + LD regimens, respectively. Only the 300 mg + LD group was predicted to provide trough concentrations above EC<sub>99</sub> (10.1  $\mu\text{g/mL}$ ) in about 50% of patients. This prediction appears to be more conservative than the observed data from the phase 2 study in which all individuals (100%) in both 100 mg and

300 mg + LD cohorts reached full receptor occupancy during the entire dosing period. This discrepancy may be attributed to the large variability of the model estimates during the recovery (or washout) phase that are most likely the consequence of a less frequent blood sampling during this period of the study.

Furthermore, this model can be used to guide future PK/PD modeling of etrolizumab for another serum PD biomarker, soluble MAdCAM-1, in UC patients. Similar to the PD profiles of the free circulating  $\beta 7$  receptor, serum-soluble MAdCAM-1, the ligand of  $\alpha 4\beta 7$  integrin, was also suppressed after etrolizumab treatment, but displayed a recovery phase after cessation of etrolizumab dosing (Figure S1).<sup>19</sup> This recovery phase mirrored the recovery profile of free circulating  $\beta 7$  receptors. Because the serum-soluble MAdCAM-1 can be measured using ELISA, a more feasible assay than the flow cytometry method used for quantifying free circulating  $\beta 7$  receptors, it is possible to use serum-soluble MAdCAM-1 as a surrogate biomarker for monitoring free  $\beta 7$  receptors in the peripheral blood. Hence, the current QSS TMDD model provides a robust foundation for developing a more sophisticated PK/PD model that is expected to simultaneously describe dynamics of serum etrolizumab level and 2 PD biomarkers, including free  $\beta 7$  receptors on the circulating intestinal homing CD4<sup>+</sup> T lymphocytes and serum-soluble MAdCAM-1. Therefore, we could potentially replace the flow cytometry (free  $\beta 7$  receptor) data used in the QSS TMDD model with the soluble MAdCAM-1 ELISA data and retain the ability to assess free circulating  $\beta 7$  receptor level via the modeling approach.

## Conclusions

The developed QSS TMDD PK/PD model adequately described the relationship between serum etrolizumab concentration and free circulating  $\beta 7$  receptors (ABS, %BL) on circulating intestinal homing CD4<sup>+</sup> T lymphocytes based on the data from a phase 1 study in patients with moderately to severely active UC. The model was able to reasonably predict the PK/PD profiles observed in the subsequent phase 2 study at specified dose regimens. This model is a useful tool to guide further PK/PD modeling and dosing regimens in future clinical trials of etrolizumab.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.