

## ARTICLE

# Population pharmacokinetic analysis of etrolizumab in patients with moderately-to-severely active ulcerative colitis

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## Abstract

Etrolizumab is an IgG1-humanized monoclonal antibody that specifically targets the  $\beta 7$  subunit of  $\alpha 4\beta 7$  and  $\alpha 4E\beta 7$  integrins, and it has been evaluated for the treatment of moderately-to-severely active ulcerative colitis (UC). Population pharmacokinetic (PK) analysis was performed to characterize etrolizumab PK properties in patients with moderately-to-severely active UC and evaluate covariate impacts on exposure. The population PK model was developed based on etrolizumab serum concentrations from patients with moderately-to-severely active UC enrolled in six studies (one phase I, one phase II, and four phase III) and validated using another phase III clinical trial. Stepwise covariate modeling was used to evaluate the impact of 23 prespecified covariates. Etrolizumab PK was best described by a two-compartment model with first-order absorption, with clearance decreasing over time. Population typical values were 0.260 L/day for clearance (CL) during the first dosing interval, 2.61 L for central volume, 71.2% for bioavailability, and 0.193/day for absorption rate. CL reduced over the study duration, the typical maximum reduction was 26% with an onset half-life of 4.8 weeks. Consequently, the predicted mean terminal half-life was shorter after a single dose (13.0 days) compared to that at steady-state (17.1 days). Baseline body weight and albumin were the most impactful covariates for etrolizumab exposure. Final population PK model well characterized the PK properties of etrolizumab in patients with moderately-to-severely active UC and identified influential covariate effects.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Etrolizumab is an IgG1-humanized monoclonal antibody that specifically targets the  $\beta 7$  subunit of  $\alpha 4\beta 7$  and  $\alpha 4E\beta 7$  integrins, and it has been evaluated for the treatment of moderately-to-severely active ulcerative colitis (UC).

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**WHAT QUESTION DID THIS STUDY ADDRESS?**

The population pharmacokinetics (PK) model well-characterized the PK properties of etrolizumab in patients with moderately-to-severely active UC and identified influential covariate effects.

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**

Etrolizumab PK was best described by a two-compartment model with first-order absorption, with clearance decreasing over time. Baseline body weight and albumin were the most impactful covariates for etrolizumab exposure.

**HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?**

This model can be used to derive individual predictions of etrolizumab PK for exposure-response analysis to inform etrolizumab dose optimization in patients with UC.

## INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that affects the colon in various patterns. UC symptoms include mucosal inflammation and ulcers, rectal bleeding, diarrhea, and abdominal pain; it may cause severe bloody diarrhea and toxic megacolon leading to surgery.<sup>1-5</sup> Dysregulation of the mucosal immune system in response to environmental factors, such as commensal microbiota, plays an important role in the pathogenesis of UC.<sup>1,2,4,5</sup> Patients with moderately-to-severe active UC currently treated with corticosteroids, immunosuppressants, or targeted therapies, such as tumor necrosis factor (anti-TNF) inhibitors, vedolizumab, tofacitinib, ozanimod, and ustekinumab. However, even with these different therapy options, there are still a large number of patients not maintaining a durable treatment response.<sup>3,6,7</sup>

Etrolizumab is an IgG1-humanized monoclonal antibody that specifically targets the  $\beta 7$  subunit of both the  $\alpha 4\beta 7$  and  $\alpha 4E\beta 7$  integrins, which regulate trafficking and retention of leukocyte/lymphocyte subsets, respectively, in the intestinal mucosa.<sup>8-10</sup> Etrolizumab does not bind to  $\alpha 4\beta 1$ , which regulates trafficking to both mucosal and non-mucosal tissues (including the central nervous system), and therefore represents a novel gut mucosal-selective anti-trafficking agent.

The objectives of this study were to develop and validate a population pharmacokinetic (PK) model for etrolizumab in patients with UC using data from seven clinical studies spanning phase I, II, and III.<sup>11-17</sup> The population PK model aimed to characterize the PK properties of etrolizumab and to assess the impact of potential clinically relevant intrinsic and extrinsic covariates on etrolizumab PK. The final population PK model predicted etrolizumab exposures for individual patients, which were used to characterize the exposure-response relationship in a sequential analysis.<sup>18</sup>

## METHODS

### Clinical trials

For this study, we used ABS4262g (phase I; NCT00694980), EUCALYPTUS (NCT01336465), HIBISCUS I/HIBISCUS II (NCT02163759/NCT02171429), HICKORY (NCT02100696), LAUREL (NCT02165215), and GARDENIA (NCT02136069) clinical trials. All clinical trial information can be accessed through the following website: <https://clinicaltrials.gov/>.

### Data and study design

A total of seven studies (1 phase I, 1 phase II, and 5 phase III) were used in the population PK development (6 studies) and external validation (1 study). A listing of the studies and key study information, including population, dosing regimen, and number of subjects treated with etrolizumab is provided in [Table 1](#). The PK assay and antidrug antibody (ADA) immunoassay were reported previously for phase I-II and III studies.<sup>13,14,17,19</sup> All studies were approved by the institutional review board or independent ethics committee and were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

### Population PK model development and covariate analysis

The population PK analysis was performed using NONMEM version 7.3.0 (ICON Development Solutions), with the first-order conditional estimation (FOCE) and the INTERACTION option.<sup>20</sup> Nonlinear mixed effects models were used to fit the concentration-time data of etrolizumab. Absolute bioavailability (F), clearance (CL), and volume of distribution (V) parameters were

**TABLE 1** Summary of etrolizumab studies included in population PK model development and external evaluation

Study	Phase	Number of subjects	Number of PK observations	Population	Dose regimen
Model development data set					
ABS4262g	I	38	537	UC (TNF Naïve and TNF IR)	SAD: 0.3, 1, 3, 10 mg/kg i.v.; 1 mg/kg <sup>a</sup> , 3 mg/kg s.c. MAD: 0.5, 1.5, 3 mg/kg s.c. Q4W until week 8; 4 mg/kg i.v. Q4W until week 8
EUCALYPTUS	II	81	609	UC (TNF Naïve and TNF IR)	105 mg SC Q4W until week 8; 420 mg s.c. week 0, 315 mg s.c. weeks 2, 4, and 8 s.c.
HIBISCUS I/HIBISCUS II	III	285	608	UC (TNF Naïve)	105 mg s.c. Q4W
HICKORY	III	509	1284	UC (TNF IR)	105 mg s.c. Q4W
LAUREL	III	350	914	UC (TNF Naïve)	105 mg s.c. Q4W
External validation data set					
GARDENIA	III	184	742	UC (TNF Naïve)	105 mg s.c. Q4W
All		1447	4694		

Note: Intravenous infusion over 1 hour in i.v. cohorts.

Abbreviations: i.v., intravenous; MAD, multiple ascending dose; PK, pharmacokinetic; Q4W, every 4 weeks; SAD, single ascending dose; s.c., subcutaneous; TNF IR, patients with inadequate response or intolerance to prior anti-TNF treatment; TNF Naïve, patients without prior anti-TNF treatment; TNF, anti-tumor necrosis factor treatment; UC, ulcerative colitis.

<sup>a</sup>No PK observations were obtained following 1 mg/kg s.c. in the phase I ABS4262g study.

estimated since data included both i.v. and s.c. administration. Based on the graphical exploratory analysis, models took into account time-dependency in CL (Figure S1).

Interindividual variability (IIV) in PK parameters were modeled as exponential random-effect models in order to constrain the individual parameter values positively, which were thus assumed to follow a log-normal distribution. IIVs were modeled as normally distributed on the logit-transformed scale to constrain values between zero and one for certain parameters (e.g., F). The residual error model was a combined additive and proportional error model (no transformation).

The covariate model was developed based on prespecified mechanistic, structural, and exploratory covariates (Table 2). Mechanistic covariates (i.e., body weight on CL and V parameters) were included in the base model based on mechanistic understanding, therefore no statistical evaluation for inclusion was performed. Body weight was chosen to represent changes in etrolizumab PK as a function of body size and was described using an allometric model with a reference weight of 70 kg.<sup>21,22</sup> The structural and exploratory covariates were evaluated using stepwise covariate model building procedure in two subsequent phases.<sup>23</sup> The structural covariates pre-assigned to evaluate were part of the design of the studies or anticipated to be major predictors explaining variability and were tested and retained in the model based on statistical significance ( $p < 0.05$  forward and  $p < 0.01$

backward) and biologically reasonable parameter estimates. The exploratory covariates were evaluated and retained in the model based on statistical significance (with more stringent criteria:  $p < 0.0001$ ) and biologically reasonable parameter estimates. For estimation of covariate coefficients, the baseline/screening value of the covariate was used, except for ADA, which was explored as time-varying, hence the actual value of the ADA covariate at the time of the observation was used and imputed if missing (imputed as negative ADA for missing baseline measurements; for missing postdose measurements, imputed by carrying forward the previous postdose ADA measurement, and, if not possible, the next ADA measurement was carried backward; if all postdose ADA observations were missing, the measurements were imputed as ADA negative). Time-varying ADA status (positive or negative) was evaluated first, if significant, time-varying ADA titers were further evaluated in place of the ADA status. Continuous covariates (e.g., albumin, C-reactive protein [CRP], fecal calprotectin [FeCal], and age) were implemented as exponential models, and categorical covariates (e.g., prior TNF- $\alpha$  antagonist therapy status, and concomitant therapy use) were entered as a fractional change in parameter value, in relation to the most common category.

The impact of covariate-parameter relationships on week-4 trough concentration based on the final population PK model was assessed in a forest plot; the uncertainty was illustrated as the 95% confidence interval (CI),

**TABLE 2** Prespecified covariates investigated during model development

Covariate type	Parameter	Covariate <sup>a</sup>
Mechanistic <sup>a</sup>	CL, Q, V <sub>c</sub> , V <sub>p</sub>	Body weight
Structural <sup>a</sup>	CL, Q, V <sub>c</sub> , V <sub>p</sub>	BMI
	CL, V <sub>c</sub> , V <sub>p</sub>	Age, sex
	CL	ADA <sup>b</sup> , ADA titer <sup>b</sup> , ALB, CRP, FeCal, LYMP, prior TNF inhibitor, CSD, IMMUS, 5-ASA
Exploratory <sup>a</sup>	CL, F, residual error	Clinical study phase (I, II, vs. III) <sup>c</sup>
	CL	Race, ethnicity, smoking status, complete MCS, MES, DISDUR, DISEXT, MAdCAM-1, AST, GFR, geographic region

Abbreviations: ADA, anti-drug antibodies; ALB, albumin; 5-ASA, concomitant aminosalicylates; AST, aspartate aminotransferase; BMI, body mass index; CL, clearance; CSD, concomitant corticosteroid; CRP, C-reactive protein; DISDUR, disease duration; DISEXT, disease extension; F, absolute bioavailability; FeCal, fecal calprotectin; GFR, estimated glomerular filtration rate; IMMUS, concomitant immunosuppressants; LYMP, lymphocytes; MAdCAM-1, mucosal addressin cell adhesion molecule 1; MCS, Mayo Clinic Score; MES, Mayo Endoscopic Subscores; Q, inter-compartmental clearance; TNF, tumor necrosis factor; V<sub>c</sub>, central volume of distribution; V<sub>p</sub>, peripheral volume of distribution.

<sup>a</sup>The baseline/screening value of the covariate was used, apart for ADA and ADA titer, which were explored as time-varying.

<sup>b</sup>Influence of ADA is assessed separately before the stepwise covariate model (SCM).

<sup>c</sup>To explore manufacturing process and pharmacokinetic (PK) assay changes between phase III and phase I/II.

based on the NONMEM covariance matrix. Reference patient's baseline values in the forest plot were assigned based on median values for continuous covariates or the most common category for categorical covariates.

## Model evaluation and external validation

Model evaluation was based on the inspection of graphical diagnostics, including goodness of fit plots and prediction-corrected visual predictive checks (pcVPC),<sup>24,25</sup> as well as changes in the objective function value provided by NONMEM, relative standard errors (RSE) and plausibility of the parameter estimate. In addition, external validation was performed using GARDENIA data.

## RESULTS

### Final population PK model

The final population PK analysis dataset included a total of 4694 PK observations from 1447 patients with moderately-to-severely active UC. The baseline demographic summaries and the observed PK profiles of the seven studies are presented in Table 3 and Figure S2.

The population PK parameter estimates of the final etrolizumab PK model are presented in Table 4. The final

population PK model was a two-compartment model with first-order absorption, and CL decreasing with time according to an exponential function (Equation 1), stepping down after each subsequent dose.

$$CL_{\text{TSFD}_j} = CL_{\text{TSFD}=0} \cdot \left( 1 - \text{Maxred} \cdot \left( 1 - e^{-\frac{\log(2)}{\text{Onset} \cdot 7} \cdot (\text{TSFD}_j - \text{TAD}_j)} \right) \right) \quad (1)$$

where TSFD is the time since first dose (in days), Maxred is the maximum reduction in CL over time, Onset is the half-life (in weeks) for the time-dependent change in CL (multiply by 7 to convert the Onset unit from weeks to days), and TAD is time after the most recent dose (in days).

IIV terms were included on F, central volume of distribution (V<sub>c</sub>), peripheral volume of distribution (V<sub>p</sub>), CL, and Maxred. The IIVs were log-normally distributed, apart for F and Maxred, where IIVs were normally distributed on the logit-transformed parameters to constrain values between zero and one. The residual variability for etrolizumab was described by a combined additive and proportional error model. The magnitude of the residual error variability was 19% lower in phase I/II studies compared to phase III studies, meaning that observations collected in phase III studies had larger unexplained variability.

Population typical value were estimated as 0.260 L/day for CL during the first dosing interval, 2.61 L for V<sub>c</sub>, 71.2%

**TABLE 3** Key baseline continuous and categorical covariate statistics for the model development

Continuous covariates	Metric	Model development data	External evaluation data
Body weight (kg)	Median (min, max)	72.2 (38.0, 216)	70.0 (40.7140)
	Mean (SD)	74.2 (18.1)	72.9 (16.8)
	<i>N</i>	1259	184
Age (years)	Median (min, max)	38.0 (18.0, 79.0)	37.0 (18.0, 76.0)
	Mean (SD)	40.2 (13.6)	39.9 (15.1)
	<i>N</i>	1263	184
Albumin (g/L)	Median (min, max)	41.0 (16.0, 56.0)	41.0 (31.0, 53.0)
	Mean (SD)	40.3 (4.27)	40.6 (3.53)
	<i>N</i>	1263	184
CRP (mg/L)	Median (min, max)	4.31 (0.140, 209)	3.26 (0.200, 130)
	Mean (SD)	10.1 (16.9)	8.43 (15.5)
	<i>N</i>	1243	180
FeCal (μg/g)	Median (min, max)	1500, (17.7, 28,800)	1300 (30.0, 28,800)
	Mean (SD)	3010 (4370)	2530 (4150)
	<i>N</i>	1119	155
MCS	Median (min, max)	9.00 (4.00,12.0)	9.00 (4.0, 12.0)
	Mean (SD)	8.87 (1.50)	8.54 (1.53)
	<i>N</i>	1262	184
Categorical covariates	Categories	<i>N</i> (%)	<i>N</i> (%)
ADA status <sup>a</sup>	Negative	976 (77)	120 (65)
	Positive	287 (23)	64 (35)
Prior TNF inhibitor	No	692 (55)	184 (100)
	Yes	571 (45)	0 (0)
DISEXT	Left-sided colitis	670 (53)	113 (61)
	Extensive/pancolitis	534 (42)	71 (39)
	Other	20 (2)	0 (0)
	Missing	39 (3)	0 (0)
Sex	Female	526 (42)	72 (39)
	Male	737 (58)	112 (61)

Abbreviations: ADA, antidrug antibody; CRP, C-reactive protein; DISEXT, disease extension; FeCal, fecal calprotectin; MCS, Mayo Clinical Score; *N*, number of subjects (for continuous, with non-missing covariate value); SD, standard deviation; TNF, tumor necrosis factor.

<sup>a</sup>ADA status by subject data.

for *F*, and 0.193/day for absorption rate of the s.c. formulation (IIV coefficient of variation: CL 24.3%,  $V_c$  25.2%, and *F* 21.1%). CL declined over study duration, eventually reaching a maximum reduction of 26% with onset half-life of 4.8 weeks, starting at administration of the second dose (i.e., after 4 weeks lag time, for Q4W multiple dosing). The illustration of typical CL versus TSFD for the empirical time-varying model is shown in Figure S3. The typical terminal half-lives after a single dose and at steady-state (95% CI) derived from the population PK parameters were 13.0 (12.2–13.9) and 17.1 (16.1–18.3) days, respectively.

In the final model, all PK parameters estimated with relatively good precision (RSE). Shrinkage was 20%–28%

for residual error and CL, however, it was substantially higher for IIV on other parameters. Therefore, eta diagnostics (e.g., displaying etas vs. covariates), were interpreted with caution.

## Covariate analysis

The CL of etrolizumab was dependent on baseline body weight, albumin, CRP, prior anti-TNF status, disease extension (left-side colitis, extensive/pancolitis, and other disease extension), and time-varying ADA titer (Table 4). The exponent for the effect of weight on CL (0.872) suggests a higher CL of etrolizumab in heavier subjects. On

**TABLE 4** Parameter estimates of the final pharmacokinetic model

Parameter	Unit	Value	RSE (%)	SHR (%)
CL	L/day	0.260	7.12	
$V_c$	L	2.61	5.82	
Q	L/day	0.449	12.9	
$V_p$	L	1.77	10.8	
F		0.712	7.35	
$k_a$	1/day	0.193	11.2	
Maxred <sup>c</sup>	Relative decline	0.263	6.70	
Onset <sup>c</sup>	weeks	4.81	12.7	
Body weight on clearance parameters <sup>a</sup>		0.872	5.58	
Body weight on volume parameters <sup>b</sup>		0.788	11.1	
Albumin on CL <sup>d</sup>	Rel. change <sup>f</sup>	-0.0314	8.79	
CRP on CL <sup>d</sup>	Rel. change <sup>f</sup>	0.00458	17.2	
Prior TNF on CL	Rel. change <sup>g</sup>	0.0490	41.8	
Extensive/pancolitis on CL	Rel. change <sup>g</sup>	0.0816	26.2	
Other disease extension on CL	Rel. change <sup>g</sup>	0.181	46.9	
Phase I and II studies on residual error <sup>e</sup>	Rel. change <sup>g</sup>	-0.192	41.0	
ADAT on CL <sup>d</sup>	Rel. change <sup>f</sup>	0.0365	27.3	
IIV CL	CV	0.243	4.68	27.7
IIV $V_c$	CV	0.252	18.0	71.1
IIV $V_p$	CV	0.262	21.2	77.6
IIV F	SD <sup>h</sup>	0.733	16.5	41.8
IIV Maxred	SD <sup>h</sup>	0.597	11.1	53.8
Proportional residual error	CV	0.196	5.53	19.9
Additive residual error	SD, $\mu\text{g/ml}$	0.427	17.0	19.9

Abbreviations: ADAT, anti-drug antibody titer; CL, clearance; CRP, C-reactive protein; CV, coefficient of variation; F, bioavailability; IIV, interindividual variability;  $k_a$ , first-order absorption rate constant; OFV, objective function value; Maxred, maximum reduction in clearance over time; Onset, half-life for the time-dependent change in CL; Q, inter-compartmental clearance; RSE, relative standard error; SD, standard deviation; SE, standard error; SHR, shrinkage; TAD, time after most recent dose; TSPD, time since first dose;  $V_c$ , central volume of distribution;  $V_p$ , peripheral volume of distribution.

<sup>a</sup>The estimate is  $\theta$  for parameters (P) CL and Q in  $\text{TVP}_i = P_{\text{population}} \cdot \left(\frac{\text{WT}_i}{70}\right)^\theta$ .

<sup>b</sup>The estimate is  $\theta$  for parameters (P)  $V_c$  and  $V_p$  in  $\text{TVP}_i = P_{\text{population}} \cdot \left(\frac{\text{WT}_i}{70}\right)^\theta$ .

<sup>c</sup> $\text{CL}_{\text{TSPD},j} = \text{CL}_{\text{TSPD}=0} \cdot \left(1 - \text{Maxred} \cdot \left(1 - e^{-\frac{\log(2)}{\text{Onset}} \cdot (\text{TSPD}_j - \text{TAD}_j)}\right)\right)$ .

<sup>d</sup>The estimate for covariate m is  $\theta$  in  $\text{Cov}_{\text{Eff}_m} = e^{\theta \cdot (\text{Cov}_m - \text{Cov}_{m,\text{ref}})}$ .

<sup>e</sup>The covariate effect is on the overall residual error (additive and proportional).

<sup>f</sup>Relative change per unit albumin, CRP, and ADAT, respectively.

<sup>g</sup>Relative change versus no prior TNF, versus left-sided colitis and versus phase III, respectively.

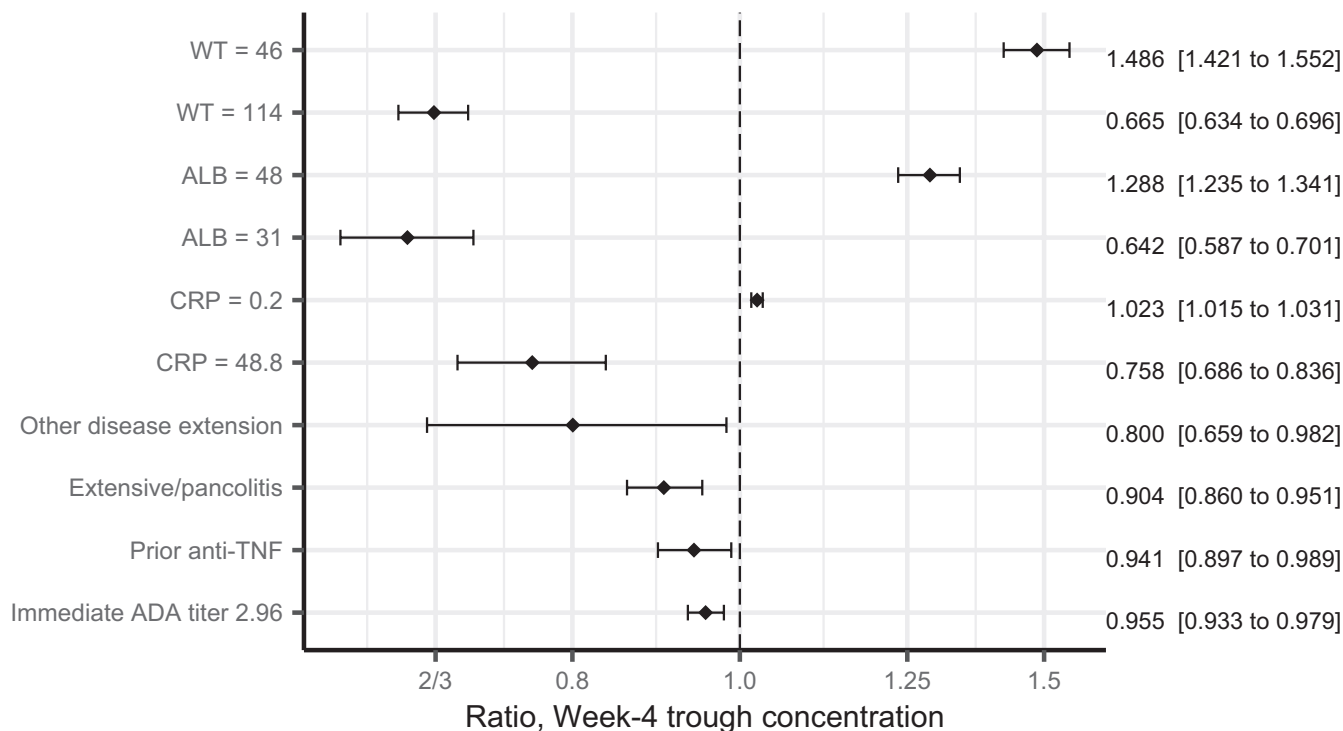
<sup>h</sup>The IIV is presented as the SD on the logit scale. The corresponding CV for F and Maxred for the final model were 0.211 and 0.440, respectively. The CV was calculated using the following approximation:  $\text{SD} = \theta \cdot (1 - \theta) \cdot \text{SD}_{\text{logit}}$  and  $\text{CV} = \frac{\text{SD}}{\theta}$ , where  $\theta$  is the typical value for F and Maxred, respectively.

the other hand, subjects with high albumin levels tend to have lower CL (relative change of -3.1% per 1 g/L albumin increase). In addition, CL increased with increasing CRP (relative change of 0.46% per 1 mg/L CRP increase), was 4.9% higher in patients that had been on prior anti-TNF therapy, was 8.2% higher in patients with extensive disease/pancolitis and 18% higher in patients with other extension (both categories vs. left-sided colitis) and increased with increasing ADA titer (relative

change of 3.7% per titer unit). The inter-compartmental clearance (Q) and volumes ( $V_c$  and  $V_p$ ) of etrolizumab were dependent on baseline body weight. The exponents for the effect of weight on Q (0.872) and on  $V_c$  and  $V_p$  (0.788) suggest higher Q,  $V_c$ , and  $V_p$  of etrolizumab in heavier subjects.

The impact of these covariates on the etrolizumab exposure (i.e., predicted week-4 trough concentration) based on the final population PK model is illustrated





**FIGURE 1** Forest plot showing the final etrolizumab pharmacokinetic (PK) model estimates of covariates effects on the week-4 trough concentration. The closed symbols represent the point estimates and the whiskers represent the 95% CI, based on the NONMEM covariance matrix. The vertical, dashed line is marking no change (a ratio of one), compared to the reference patient. The x-axis is on log scale, and ratios 2/3 and 1.5 are of corresponding impact, just as ratios 0.8 and 1.25 are. For continuous covariates, the impact has been shown for the 2.5th and 97.5th percentile of the covariate (across the subjects in the PK analysis and external evaluation data set). In particular, for ADA titer, the 2.5th and median value were both zero titer (i.e., the reference) and therefore only positive titer was illustrated. The positive titer here represents the 97.5th percentile across subject's first post-dose observation, among all subjects that had a postdose observation before week 6 (1443 out of 1447 subjects). The numbers on the right hand of the plot represent point estimates [95% CIs] of the ratio to the reference patient (with baseline values: 72 kg body weight, 41 g/L albumin, and 4.23 mg/L CRP, being a patient in phase III without prior anti-TNF, with left-sided colitis, who was ADA negative [at least] until week 4). ADA, anti-drug antibodies; ALB, albumin; CI, confidence interval; CRP, C-reactive protein; Immediate ADA titer 2.96: 97.5th percentile ADA titer value (2.96) across patients close to week-4 (PK sampling time) given ADA titers were varying over time; TNF, tumor necrosis factor; WT, body weight.

in the forest plot (Figure 1). Baseline body weight and albumin are the most impactful covariates for etrolizumab exposure.

### Final population PK model evaluation and external validation

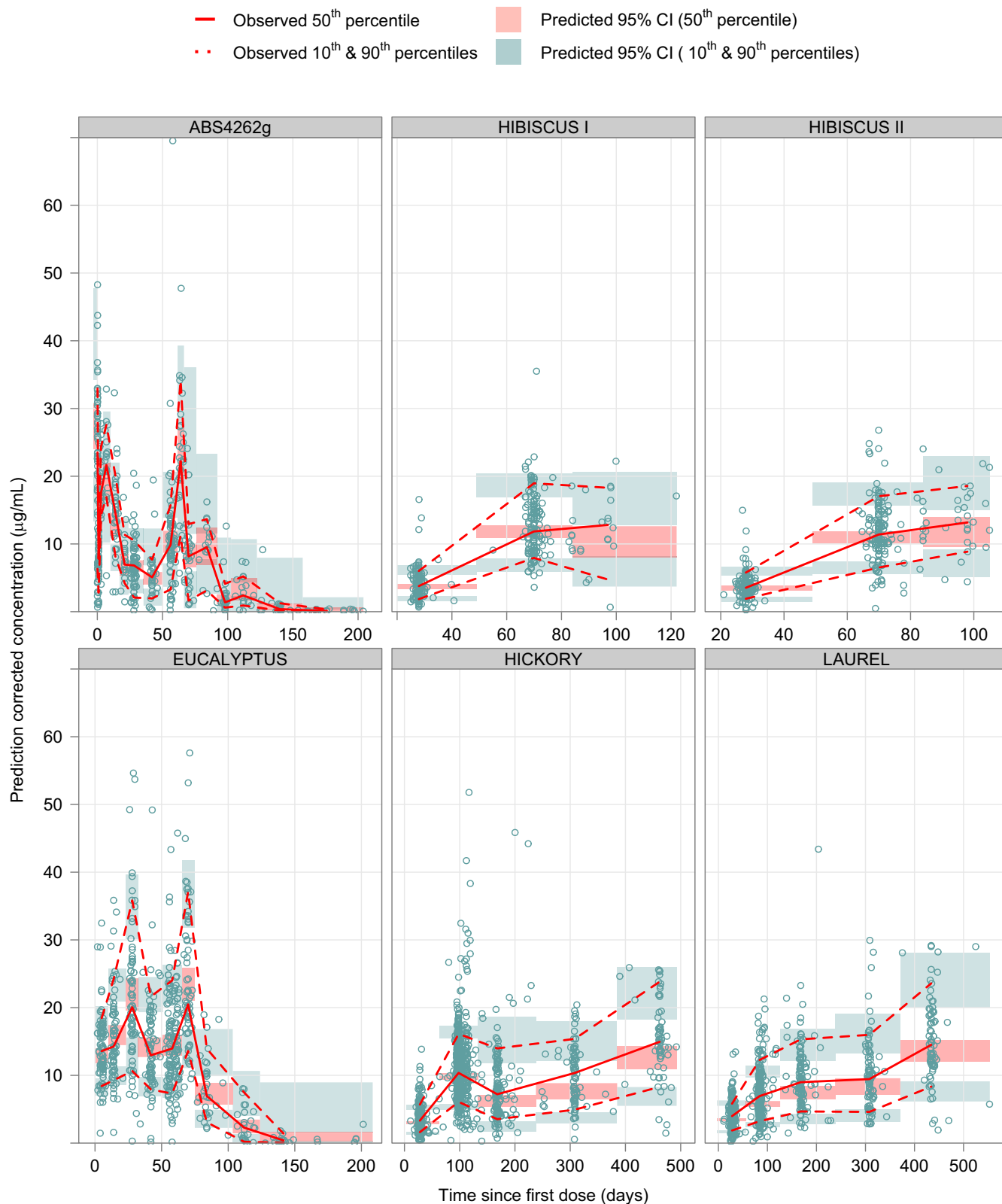
The model evaluation (pcVPC) of etrolizumab concentration versus TSFD, stratified by study, is presented in Figure 2. The observed concentrations were reasonably well-described by the model. The goodness-of-fit plots also showed that the predictions from the final model were generally consistent with the observed data (Figure S4).

The external evaluation of etrolizumab concentrations versus time, based on data from GARDENIA, validated the model (Figure 3) with the observed concentrations being reasonably well-described by the model (median as well as 80% prediction interval).

## DISCUSSION

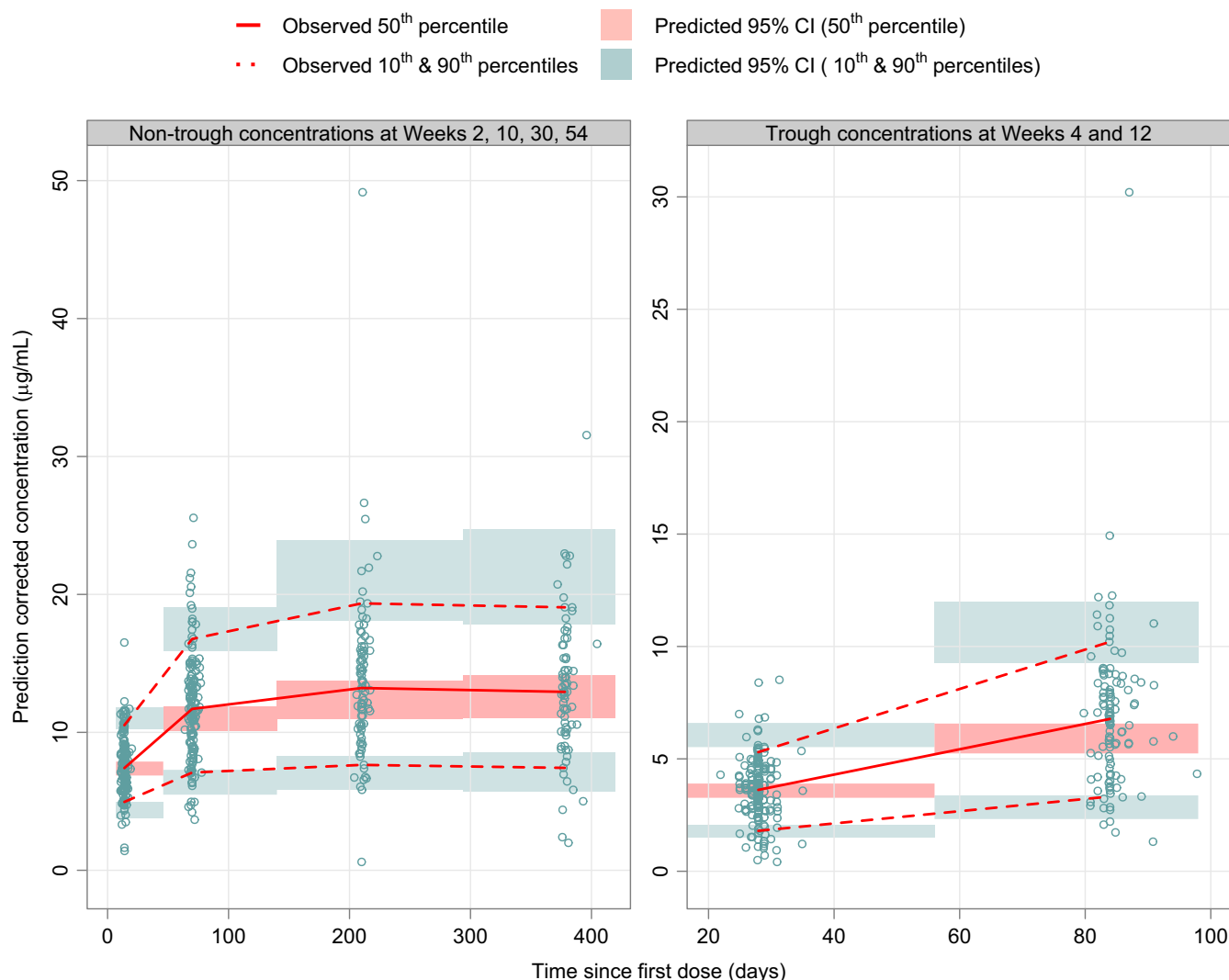
The concentration–time profiles of etrolizumab in patients with UC were adequately described by a two-compartment disposition model with first-order absorption, with clearance decreasing over time. Given that the clearance of etrolizumab decreases over time (Equation 1), the predicted mean terminal half-life was shorter after a single dose (13.0 days) compared to that at steady-state (17.1 days).

Baseline body weight, albumin, CRP, prior anti-TNF status, disease extension (left-side colitis, extensive/pancolitis, and other disease extension), and time-varying ADA titer were identified as statistically significant covariates of CL, whereas body weight was also identified as a statistically significant covariate of  $V_c$ ,  $V_p$ , and  $Q$ . However, these covariates combined only accounted for a small portion of IIV for CL (21.4%) and  $V_c$  (4.91%), indicating their impact on overall etrolizumab PK



**FIGURE 2** Prediction corrected visual predictive check of etrolizumab concentrations versus time since first dose, for the final population pharmacokinetic model, stratified by study. Etrolizumab concentrations are displayed versus time since first dose. The solid and dashed red lines represent the median, 10<sup>th</sup> and 90<sup>th</sup> percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval (CI) of the median, 10<sup>th</sup> and 90<sup>th</sup> percentiles predicted by the model. The observed data are indicated by open circles.





**FIGURE 3** Prediction corrected visual predictive check of etrolizumab concentrations, for GARDENIA (external evaluation) based on the final population pharmacokinetic model. Etrolizumab concentrations are displayed versus time since first dose, on linear scale, stratified for trough and non-trough samples. Observations collected at safety follow-up, unscheduled, early termination visits, and at ulcerative colitis flare events are not included. The solid and dashed red lines represent the median, 10th, and 90th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval (CI) of the median, 10th and 90th percentiles predicted by the model. The observed data are indicated by open circles.

exposure may be limited. As shown in Figure 1, baseline body weight and albumin are the most impactful covariates for etrolizumab exposure, and higher CRP was associated with lower exposure, whereas all other covariate effects are mild with the ratio over the reference subject within  $\pm 20\%$ . Other disease extension appears to have a  $-20\%$  impact on exposure (i.e., trough concentration at week 4), but it has large uncertainty due to limited patients in this group (2% of the data). The lower magnitude of the residual error variability found for the phase I and II data compared to phase III data is expected, because earlier phase clinical studies may be better controlled for both treatment adherence and timing of PK samples. Clinical studies phases (I/II vs. III) were also tested on CL and F, but it showed no

effect on CL or bioavailability, meaning that manufacturing process and/or PK assay changes have minimal impact on etrolizumab PK.

The influence of the disease activity marker albumin on clearance (decreasing CL with increasing albumin) is in line with previous observations for monoclonal antibodies, for example, vedolizumab, a monoclonal antibody that targets  $\alpha 4\beta 7$  integrin, and other monoclonal antibodies in this disease area, such as infliximab.<sup>26–28</sup> The influence of the second disease activity marker identified, CRP (increasing CL with increasing CRP), has also been assessed for both vedolizumab and infliximab.<sup>26,28,29</sup> Both albumin and CRP have been identified as a predictor for monoclonal antibody clearance in inflammatory disease.<sup>27,30</sup> Furthermore, the increase in clearance due to occurrence of ADA, which

was estimated in the final population PK model using the ADA titer, is a well-known observation for monoclonal antibodies. However, the occurrence of ADA appeared to have a very mild effect for etrolizumab with 3.7% relative change in CL per unit ADA titer (Table 4), also illustrated in Figure 1 by the minimal impact on week-4 trough concentration compared to other statistically significant covariates. The finding of a slightly higher clearance in patients that had been on prior anti-TNF (4.9%) has been observed for vedolizumab (4% higher clearance).<sup>31</sup> The effect of disease extension on CL may require further elucidation. Although patients with greater disease extent, such as extensive/pancolitis in phase III, had 8.2% increase in CL (compared to the left-sided colitis), it is difficult to distinguish increased clearance due to disease extent versus due to persistent inflammation at the end of induction, either of which can result in a “leaky” gut and higher clearance.

The maximum reduction in clearance with time was 26% with an onset half-life of 4.8 weeks, with onset initiation after the second dose administered (i.e., clearance constant before). The time-dependent clearance may reflect patients' improvement in the disease over time. Generally, with less inflammation, albumin levels increase, and the change in albumin levels therefore serve as a marker of disease status. In the current model, only baseline values of albumin and CRP were assessed, as a result, time may be viewed as an indirect measure of changes in albumin over time. Models with time-varying covariates (i.e., albumin and/or CRP), instead of an empirical time-varying CL, were also explored, but they were not able to fully describe the extent of CL change over time. Potential explanations for not identifying the time-varying covariates as predictors of time-varying CL may include: (1) the time-varying covariate data (CRP and albumin) reflecting the inflammation level cannot fully explain the overall changes in PK over time, and/or (2) the time-varying covariate data were sparsely sampled compared with the PK data sampling, which limits their ability to capture the PK changes over time. One explanation for the time-dependent changes may be a reduced leakiness of the gut, related to improvement in the disease, which may lead to a lower elimination of albumin and etrolizumab via feces as hypothesized for infliximab.<sup>32</sup> An alternative or additional suggested mechanism behind the inverse relationship between clearance and albumin is that albumin, just as IgG monoclonal antibodies, interacts with (bind to) the neonatal Fc receptor, which is of importance for the protection against elimination of monoclonal antibodies via internalization, leading to the long half-life of albumin and IgG monoclonal antibodies. Therefore, in the more severe disease status, the low albumin levels could reflect a lower number of neonatal Fc receptors, leading to

less internalization and then an increase in etrolizumab clearance.<sup>33</sup>

In summary, the final population PK model adequately characterized the PK properties of etrolizumab in patients with moderately-to-severely active UC and identified influential covariate effects. The final model was a two-compartment model with first-order absorption, and CL decreasing with time according to an exponential function, stepping down after each subsequent dose. The identified covariate relationships were, in general, anticipated: volumes and clearances increased with increasing body weight. CL decreased with increasing albumin or decreasing CRP, and CL was higher in patients that had been on prior TNF inhibitors and was higher in patients with extensive disease/pancolitis and other extension (vs. left-sided colitis). Model diagnostics for the final population PK model exhibited satisfactory predictive performance for etrolizumab. The external evaluation based on data from GARDENIA provided further reassurance, as the final population PK model described GARDENIA data reasonably well, which supports the model usability to derive individual predictions of etrolizumab exposure for exposure-response analysis.

#### AUTHOR CONTRIBUTIONS

A.M., R. Zhu, S.J., and J.R. wrote the manuscript. R. Zhu, A.M., W.Z., M.T.T., Y.S.O., T.L., R.B., N.K., and G.S. designed the research. S.J., J.R., A.M., and R. Zhu performed the research. S.J., A.M., and R. Zhang analyzed the data.

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#### CONFLICT OF INTEREST

A.M., T.L., N.K., W.Z., G.S., R. Zhang, R.B., and R. Zhu are Genentech employees and Roche shareholders. M.T. and Y.S.O. were employees of Genentech and Roche shareholders at the time of this work. S.J. and J.R. are Pharmetheus AB employees working under contract with Genentech.

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### SUPPORTING INFORMATION

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