

# Population Pharmacokinetic Analysis of Certolizumab Pegol in Patients With Crohn's Disease

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## Abstract

Certolizumab pegol (CZP), an anti-tumor necrosis factor  $\alpha$  agent, is an effective therapy for Crohn's disease (CD). A population pharmacokinetic (PK) analysis of subcutaneously administered CZP was performed using data from 2157 CD patients from 9 separate studies. The aim was to determine which covariates influence the disposition of CZP. The final CZP population PK model consisted of a baseline, first-order absorption, and 1-compartment disposition. CZP antibodies were treated as a structural model covariate and caused apparent clearance (CL/F) to increase from 0.685 to 2.74 L/day. Body surface area (BSA) influenced both CL/F and apparent volume of distribution (V/F) in a linear fashion; both parameters increased by more than 53% and 49%, respectively, across the range of BSA measurements in the data. Albumin influenced CZP CL/F in a nonlinear fashion; CL/F decreased from 1.05 to 0.613 L/day with increasing albumin concentrations in antibody-negative patients. C-reactive protein (CRP) had a borderline influence and CL/F increased by more than 20% across the range of CRP measurements in the data set. Race had a minor influence on V/F. The determined covariates' impact on CZP disposition may be of clinical utility in CZP therapy of CD patients when the PK/pharmacodynamic relationship becomes available.

## Keywords

certolizumab pegol, Crohn's disease, NONMEM, covariates, anti-TNF

Certolizumab pegol (CZP) is an engineered, pegylated FAb' fragment of a humanized tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) inhibitor monoclonal antibody. One of its indications is for reducing signs and symptoms of Crohn's disease (CD) and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy.

Recent reviews of the therapy of immune diseases with monoclonal antibodies<sup>1,2</sup> have stated that little is known about the exposure–response relationships in this class of drugs or the factors that may affect their disposition. Potential factors cited that may influence response included immunogenicity, sex, body size, disease severity, and serum albumin, among others.<sup>2</sup> A population pharmacokinetic (PK) analysis of infliximab data from 274 patients with active ankylosing spondylitis<sup>3</sup> found that the presence of antibodies to infliximab was associated with approximately 60% higher infliximab clearance (CL); no other covariates were detected. An additional population PK analysis of infliximab performed in 482 patients with ulcerative colitis<sup>4</sup> found that clearance was higher in patients who developed antibodies and was inversely related to serum albumin concentrations. In addition, the volume of the central compartment was found to increase with increasing weight.

Currently, the information about factors that may influence the disposition of TNF- $\alpha$  inhibitors is limited. If and when potential covariates that influence the PK of TNF- $\alpha$  inhibitors are identified, then this information would provide a means to understanding and possibly controlling the between-patient variability in PK.

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The present report is a population pharmacokinetic analysis of a large CZP data set obtained from CD patients who participated in 9 separate clinical studies and represents, to our knowledge, the first report of potential covariates that may influence the disposition of CZP.

## Methods

CZP PK data after subcutaneous administration were available from 9 studies carried out in 2157 CD patients; C87005,<sup>5</sup> C87031,<sup>6</sup> C87032,<sup>7</sup> C87037, C87042,<sup>8</sup> C87043,<sup>9</sup> C87047, C87048, and C87085.<sup>10</sup> CZP was administered at doses of 100, 200, or 400 mg, given once every 2 or every 4 weeks. The 9 studies are summarized in Table 1. Multiple blood samples for determinations of CZP concentrations were obtained after both single and multiple dosing.

A sandwich enzyme-linked immunosorbent assay (ELISA) was used to measure the concentration of CZP. Microtiter plates were precoated with recombinant human TNF- $\alpha$ , which bound to the CZP that was present in the plasma sample. Bound CZP was revealed by the use of a polyclonal goat anti-human kappa antibody, labeled with horseradish peroxidase, followed by 3',5,5' tetramethylbenzidine substrate. The reaction was stopped with 2.5 M H<sub>2</sub>SO<sub>4</sub>, and the absorbance read at 450 nm (reference, 630 nm). The absorbance was proportional to the amount of CZP in the plasma sample. Calibration of

the assay was achieved by the use of a set of CZP standards prepared in phosphate-buffered saline (PBS)/bovine serum albumin over the range of 1.4 to 1000 ng/mL. Plasma samples were prediluted at least 1:100 in PBS/1% bovine serum albumin prior to the assay. The lower limit of quantification (LLOQ) for this assay, allowing for a sample dilution of 1/100, was 0.41  $\mu$ g/mL.

Anti-CZP antibodies were measured using a screening ELISA-based technique that has a double antigen sandwich (bridge) format to allow detection of all classes of antibodies from humans. Microtiter plates were precoated with CZP, which binds the anti-CZP antibodies present in the plasma sample. Standards or PBS/0.1% Tween 20/1% bovine serum albumin followed by interassay controls or sample were added to the required number of wells on a microtiter plate in duplicate. After incubation, the plate was then washed twice with PBS/0.1% Tween 20 and tapped dry. Biotinylated CZP was added to the wells to bind to the captured anti-CZP antibodies. After incubation, the plate was again washed twice with PBS/0.1% Tween 20 and then tapped dry. Streptavidin-horseradish peroxidase was added to the wells to bind to the bound biotin conjugate. After incubation the plate was washed 4 times with PBS/0.1% Tween 20 and tapped dry. In the final incubation step, a horseradish peroxidase substrate tetramethyl benzidine was added to the wells and was incubated. The reaction was stopped with 2.5 M H<sub>2</sub>SO<sub>4</sub> and the absorbance read at 450 nm (reference, 630 nm). Absorbance was proportional

**Table 1.** Summary of Studies and Data

Study	Dosing Regimen	Number of Subjects	Total Subjects	Number of PK Samples
C87005 (5)	100 mg Q4W (3 doses)	74	219	1334
	200 mg Q4W (3 doses)	72		
	400 mg Q4W (3 doses)	73		
C87031 (6)	400 mg at weeks 0, 2, 4, 6, 12, 16, 20, and 24	329	331	2287
C87032 (7)	400 mg at weeks 0, 2, 4, 6, 12, 16, 20, and 24	436	668	3398
C87037	200 mg Q2W (3 doses)	2*	3	11
	400 mg Q2W (3 doses)	1*		
C87042 (8)	400 mg at weeks 0, 2, 4, then 400 mg Q2W to week 24, or 400 mg Q4W to week 24	536	539	4789
		186		
		187		
C87043 (9)	400 mg at weeks 0, 2, 4, then 400 mg Q4W decreasing in interval to Q2W in subjects with lack/loss response	84	88	288
C87047 (follow on from C87037)	400 mg Q4W at weeks 8, 12, 16, 20, and 24	40*	40	370
C87048 (follow on from C87037)	400 mg Q2W at weeks 8, 10, 12, then 400 mg Q4W at weeks 16, 20, 24, 28, and 32	46*	46	475
C87085 (10)	400 mg at weeks 0, 2, and 4	218	223	609
<b>Total</b>			<b>2157</b>	<b>13 561</b>

Q4W, every 4 weeks; Q2W, every 2 weeks; PK, pharmacokinetics.

\*Studies C87047 and C87048 were both follow-on studies of study C87037, hence, the low numbers of CD patients listed in study C87037.

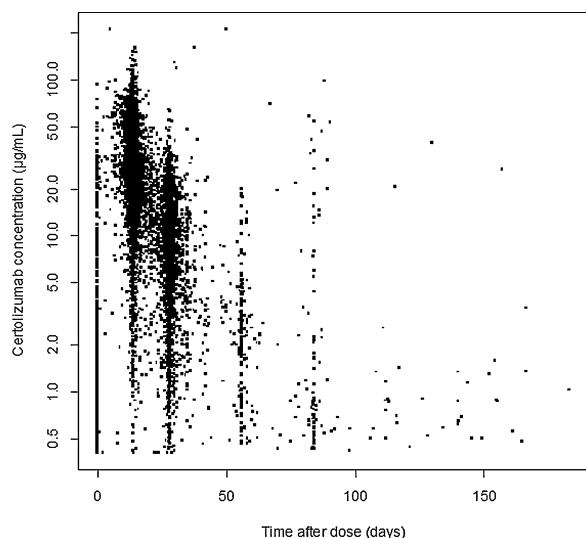
to the amount of anti-CZP antibodies present in the plasma sample. Quantification was achieved by calibration with an affinity-purified rabbit anti-CZP standard curve (range, 0.03–2.00  $\mu\text{g/mL}$ ). Plasma samples were diluted 1:10 for the assay, with results expressed as units per milliliter, where 1 unit is equivalent to 1  $\mu\text{g/mL}$  of the rabbit standard. The LLOQ for this assay, allowing for the sample dilution, was 0.06 units/mL (0.6 units/mL undiluted samples). Samples were classified as antibody positive if the concentration of antibodies was  $>2.4$  units/mL.

The total number of CZP concentrations used was 13 561; the median number of PK samples per patient was 6 and ranged between 1 and 17. Antibodies to CZP were detected in 139 patients who contributed 270 CZP antibody-positive concentrations.

The CZP PK data versus time after dose are shown graphically in Figure 1. In many of the patients ( $n = 525$ ) positive predose CZP concentrations were detected (median, 1.18  $\mu\text{g/mL}$ ; range, 0.41–93.4  $\mu\text{g/mL}$ ). This is likely because of prior anti-TNF therapy and was not considered a covariate to be tested on CL/F.

The covariates available for testing included presence of anti-CZP antibodies, body weight (WT), body surface area (BSA), body mass index (BMI), sex, age, race, albumin, C-reactive protein (CRP), creatinine clearance (CrCL), lymphocyte count, use of immunosuppressants, and Crohn's Disease Activity Index (CDAI). Baseline values were used for all the covariates except presence of CZP antibody-positive concentrations. CZP antibody-positive concentrations were used as present/absent per individual CZP concentration.

Baseline covariate information was missing for some of the 2157 patients: CDAI ( $n = 19$ ), CRP ( $n = 29$ ), and baseline lymphocyte count ( $n = 64$ ). The missing values



**Figure 1.** Certolizumab concentration versus time after dose, for all 9 studies (linear scale).

**Table 2.** Summary of Continuous and Categorical Covariates

Covariate*	Mean	Median	Min	Max	SD
<b>Continuous</b>					
Age (years)	37	35	16	80	12
Weight (kg)	69	65	31	151	17
BMI ( $\text{kg/m}^2$ )	24	23	13	56	5
BSA ( $\text{m}^2$ )	1.8	1.8	1.2	2.7	0.2
CrCL ( $\text{mL/min}$ )	112	107	25	283	2
CRP ( $\text{mg/L}$ )	20	8	0.1	286	28
Albumin ( $\text{g/L}$ )	41	41	17	52	5
Lymphocytes ( $10^9/\text{L}$ )	1.6	1.5	0.1	6.5	0.8
CDAI	302	290	75	583	63
<b>Categorical</b>					
	Category	n			
CZP antibodies	Present	270			
	Absent	13 291			
Sex	Female	1198			
	Male	959			
Race	White	1964			
	Black	29			
	Asian	11			
	Indian	17			
	Hispanic	5			
	Japanese	89			
Immunosuppressant use	No	1268			
	Yes	889			

BMI, body mass index; BSA, body surface area; CrCL, creatinine clearance; CRP, C-reactive protein; CDAI, Crohn's Disease Activity Index; CZP, certolizumab pegol.

\*Covariate summary values are given at patient level except for CZP antibodies, which are given at the level of the total number of CZP concentrations.

were imputed with the median of the remaining patients: 290 for CDAI, 8  $\text{mg/L}$  for CRP, and  $1.5 \times 10^9/\text{L}$  for lymphocyte count.

The covariates are summarized in Table 2.

### Population Pharmacokinetic Model Development

The CZP PK data were Ln-transformed prior to analysis using NONMEM 7.2.0.<sup>11</sup> The structural form of the basic population model was established first, and 1- and 2-compartment models with baseline and first-order absorption were tested; the 1-compartment model was selected. The baseline parameter was included because a large number of subjects had measurable pre-first dose concentrations and concentrations at the later times did not fall back below the LLOQ in some of the concentration–time-rich data profiles. Intersubject variability (IIV) was included for all parameters for which its estimation was supported. The presence of CZP antibody-positive concentrations was considered a structural model covariate and was therefore included during the development of the basic population PK model as a binary covariate. A proportional error model was used (additive on the Ln scale).

Comparison between various potential models was partly based on a likelihood ratio test based on the difference in the NONMEM-provided objective function value for 2 hierarchical competing models and where the degrees of freedom are equal to the difference in parameter numbers between 2 models. Visual assessment of goodness-of-fit (GOF) plots and the condition number<sup>12</sup> were also used to inform the model selection process.

### Covariate Model Building

Once the basic CZP population PK model had been developed, a covariate analysis was performed using the stepwise covariate model module of Perl speaks NONMEM, version 3.4.2.<sup>13,14</sup>

Covariate model building was carried out in 2 stages. In the first stage, models that looked at the potential influence of WT, BSA, and BMI were evaluated to establish which size measure was most appropriate to carry forward to the full covariate analysis. In the second stage, a full covariate analysis was performed using the selected size measure and all remaining covariates.

In both stages of covariate selection, forward covariate selection was performed using a  $P$  value of  $< .01$  ( $\chi^2_{P = .01, df = 1} = 6.63$ ), and backward deletion was performed using a  $P$  value of  $< .001$  ( $\chi^2_{P = .001, df = 1} = 10.83$ ) as the selection criterion. Finally, a clinical relevance criterion was applied that was set as a change greater than 25% across the 5th to the 95th percentiles of the covariate range in the data set. Covariates were only to be retained after the backward deletion step if they met the clinical relevance criterion. The magnitude of the 25% change in parameter values was selected because the potential for modifying CZP dose based on covariates is currently limited to doubling or halving dose frequency.

The potential influence of the covariates was evaluated on CL/F and apparent volume of distribution (V/F).

### Population Pharmacokinetic Model Qualification

The GOF plots and a visual predictive check (VPC) were used to evaluate the predictive performance of the CZP population PK model. The VPC evaluates capacity to simulate the same data that were used for the model development. Plasma concentrations of CZP were simulated 100 times using the dose and covariate data from the subjects who were used in the model development data set, using the same sampling times; the simulated data were then graphically compared with the observed data.

## Results

### Basic Population Pharmacokinetic Model

The basic CZP population PK model, composed of first-order absorption and 1-compartment disposition with a

baseline parameter; the model, was parameterized as a first-order rate constant for absorption (KA), CL/F, V/F, and baseline. The 1-compartment model was selected because a successful minimization step was not obtained for the 2-compartment model. IIV was included in all parameters. A proportional residual error model was used, and the final residual variability was estimated to be 34.6%.

The basic CZP population PK model included the influence of CZP antibody-positive concentrations on CL/F, and IIV for both CL/F and baseline. The inclusion of CZP antibody-positive concentrations was highly statistically significant and resulted in drops in objective function value of 128, 47, and 126, for CL/F, IIV on CL/F, and IIV on baseline, respectively ( $P < .001$  for all 3 parameters). Inclusion of the presence of CZP antibody-positive concentrations on the remaining model parameters was not statistically significant ( $P > .05$ ).

### Covariate Model Building

In the first stage of covariate model building, of the 3 different size measures, WT, BMI, and BSA, the latter was found to best describe the influence of size on CL/F and V/F; linear models were selected for both parameters. No influence of any size parameter was found on KA. Consequently, only BSA was included in the second stage of full covariate testing on CL/F and V/F.

In the forward covariate selection step of the full covariate model building, albumin, BSA, CrCL, and CRP were found to influence CL/F, and BSA and race were found to influence V/F ( $P < .01$ ). All covariates remained statistically significant during the backward deletion step ( $P < .001$ ).

Finally, the clinical relevance criterion that the parameter that the covariate influenced should change by greater than 25% was applied. With respect to the continuous covariates, the change in the affected parameter was calculated using the 5th and 95th percentiles of the covariate range to avoid potentially extreme covariate values influencing the decision regarding the clinical relevance criterion. With respect to the influence of race on V/F, the categories Other (16% change), Indian Asian (8% change), and Hispanic (-3% change) were merged with the white category. The influence of CrCL on CL/F was also removed (17% change in CL/F between a CrCL of 66 to 172 mL/min). CRP was found to have a borderline influence and CL/F increased by more than 20% across the range of CRP measurements in the CD patients' data set. Although the clinical relevance criterion was not met for CRP, this effect was retained in the final model because the effect of CRP had been estimated to be larger in prefinal models.

The final covariate model found that BSA influenced CL/F and V/F in a linear fashion for both parameters;

albumin and CRP were both found to influence CL/F in nonlinear relationships. Race (Japanese, black, and Asian categories only) was found to influence V/F.

### Final Population Pharmacokinetic Model

The parameter estimates for the final CZP population PK model are presented in Table 3. The equations showing how CL/F and V/F are influenced by the various covariates are provided below Table 3.

CZP was administered subcutaneously. Relatively little PK data were collected during the absorption process, meaning that a simple first-order process was

sufficient to describe absorption. The half-life associated with the absorption of CZP in typical CD patients was calculated to be 3.5 days, which means that it took 17.5 days for 97% of the CZP to be absorbed.

The presence of CZP antibody-positive concentrations had a profound effect on CL/F, causing it to increase from 0.685 to 2.74 L/day. Unsurprisingly, the change in CL/F in the presence of CZP antibody-positive concentrations also caused an increase in the IIV for CL/F, which was estimated to be 27.5% and 83.6% in the absence and presence of CZP antibody-positive concentrations, respectively. The difference in the variability between the 2 groups was a result of when a patient was identified as antibody positive. There were varying degrees of the anti-CZP antibodies' impact on PK (minimal versus complete elimination of CZP concentrations). In contrast, in an antibody-negative patient, there was no effect and minimal between-subject variability associated with this category. The half-lives of elimination of CZP in typical CD patients, in the absence and presence of CZP antibody-positive concentrations, were calculated to be 8 and 2 days, respectively.

The linear relationship found between CL/F and BSA was such that CL/F in antibody-negative patients increased from 0.534 to 0.896 L/day over the 5th to 95th percentiles of the BSA range in the data (78% to 131% of the CL/F of a typical antibody-negative CD patient with a BSA of 1.76 m<sup>2</sup>). The linear relationship between V/F and BSA in the final population PK model was such that V/F in antibody-negative patients increased from 6.06 to 9.75 L over the 5th to 95th percentiles of the BSA range. The influence of BSA on the CZP concentration-versus-time profile for low and high BSA values is illustrated in Figure S1.

The influence of albumin and CRP on CL/F is illustrated in Figure 2. The nonlinear relationship between CL/F and albumin (Figure 2, bottom) was such that CL/F decreased steeply with increasing albumin concentrations below 41 g/L and decreased less steeply when albumin concentrations were higher than 41 g/L. Over the 5th to 95th percentiles of the albumin data range, CL/F in antibody-negative patients decreased from 1.05 to 0.613 L/day, which was 154% to 89% of the CL/F in a typical antibody-negative CD patient with an albumin level of 41 g/L.

The nonlinear relationship between CL/F and CRP (Figure 2, top) showed that CL/F increased with increasing CRP, up to a CRP value of 8 mg/L. Thereafter, the relationship between CL/F and CRP was almost flat. CL/F in antibody-negative patients increased from 0.574 to 0.712 L/day over the 5th to 95th percentiles of the CRP data range, which was 86% to 104% of the CL/F in a typical antibody-negative CD patient with a CRP of 8 mg/L.

Race was found to influence V/F in the final population PK model. Initially, all race categories were allowed to

**Table 3.** Certolizumab Population PK Parameter Estimates for the Final Model

Parameter	Estimate	SE (%)
<b>Structural model</b>		
KA (/day), $\theta_1$	0.200	0.01
CL/F, ATB -ve (L/day), $\theta_2$	0.685	1.6
CL/F, ATB +ve (L/day), $\theta_5$	2.74	11.4
V/F (L), $\theta_3$	7.61	1.4
Baseline ( $\mu\text{g/mL}$ ), $\theta_4$	1.23	4.1
Albumin?(1) on CL, $\theta_7$	-0.0598	7.1
Albumin?(2) on CL, $\theta_8$	-0.0177	18.1
BSA on CL, $\theta_9$	0.715	5.1
CRP?(1) on CL, $\theta_{10}$	0.0205	13.8
CRP?(2) on CL, $\theta_{11}$	0.000561	64.2
BSA on?V, $\theta_{12}$	0.656	8.1
RACE?(J) on?V, $\theta_{13}$	-0.250	15.5
RACE?(B) on?V, $\theta_{14}$	0.265	52.0
RACE?(A) on?V, $\theta_{15}$	0.415	65.0
<b>IIV (%CV)</b>		
CL/F (ATB -ve)	27.5	4.1
CL/F (ATB +ve)	83.6	25.7
V/F	16.7	20.3
KA	50.1	9.4
Baseline (ATB -ve)	95.1	5.4
Baseline (ATB +ve)	72.3	10.9
<b>Residual error</b>		
Proportional error (%) (additive on Ln scale), $\theta_6$	34.6	0.3

ATB = 0 in the absence of antibodies, ATB = 1 in the presence of antibodies.

If CRP  $\leq$  8, CL\_CRP =  $(1 + \theta_{10} \times [\text{CRP} - 8])$

If CRP > 8, CL\_CRP =  $(1 + \theta_{11} \times [\text{CRP} - 8])$

If albumin  $\leq$  41, CL\_ALB =  $(1 + \theta_7 \times [\text{albumin} - 41])$

If albumin > 41, CL\_ALB =  $(1 + \theta_8 \times [\text{albumin} - 41])$

CL/F =  $([1 - \text{ATB}] \times \theta_2 + \text{ATB} \times \theta_5) \times \text{CL\_CRP} \times \text{CL\_ALB} \times (1 + \theta_9 \times [\text{BSA} - 1.76])$

VRACE = 1; for RACE = 1, 4, 6, 7 (nobody in cat 5) – whites, Other, Indian Asians, and Hispanics

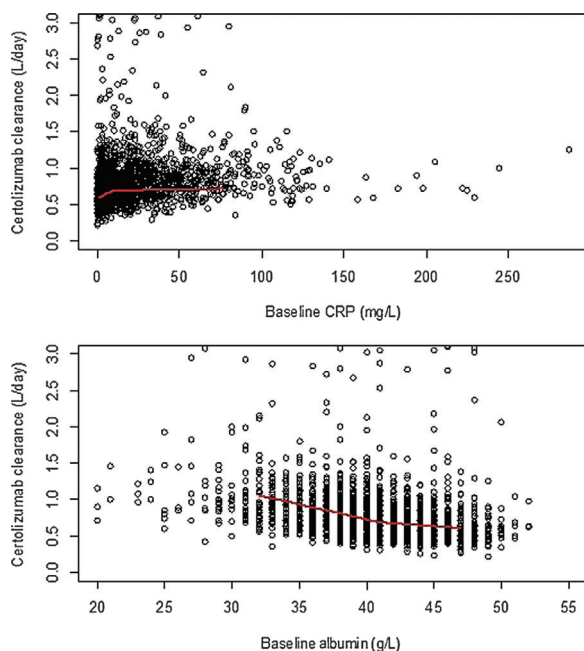
IF?(RACE.EQ.8) VRACE =  $(1 + \theta_{13})$  – Japanese

IF?(RACE.EQ.2) VRACE =  $(1 + \theta_{14})$  – Black

IF?(RACE.EQ.3) VRACE =  $(1 + \theta_{15})$  – Asian

V/F =  $\theta_3 \times \text{VRACE} \times (1 + \theta_{12} \times [\text{BSA} - 1.76])$

KA, constant for absorption; CL/F, apparent clearance; V/F, apparent volume of distribution; BSA, body surface area; CRP, C-reactive protein; ATB -ve, antibody negative; ATB +ve, antibody positive.



**Figure 2.** The estimated relationships (red lines) for the influence of albumin (bottom) and CRP (top) on CL/F. The estimated relationships are superimposed on data (open black circles) from the basic population PK model, in which covariates were not included. The red lines span the 5th to the 95th percentiles of the covariate ranges. The y-axis has been curtailed, so outlying CL/F values are not included. CL/F, apparent clearance; CRP, C-reactive protein; PK, pharmacokinetics.

differ independently from the white category. However, the differences for the Other, Indian Asian, and Hispanic races did not meet the clinical relevance criterion, and so these categories were combined with the white category in the final population PK model. V/F for the typical black and Asian CD patient was estimated to be 26.5% (95%CI, -0.5% to 53%) and 41.5% (95%CI, -11% to 94%) higher, respectively, than for whites, whereas V/F for the typical Japanese CD patient was estimated to be 25.0% (95%CI, 17% to 33%) lower than for whites.

#### Population Pharmacokinetic Model Qualification

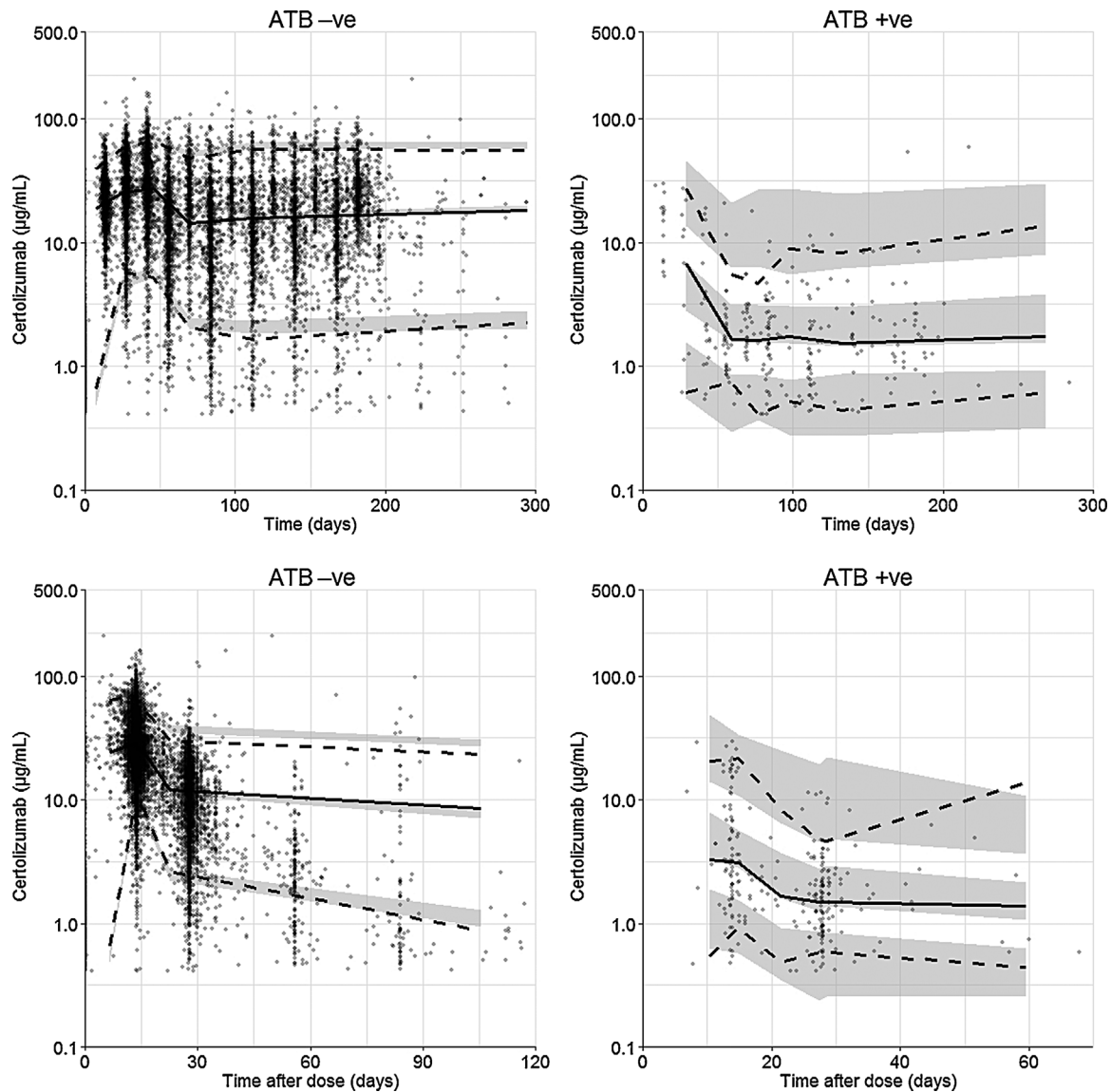
The GOF plots for both the basic and final CZP population PK models showed that the models described the data well (not shown). The VPC for the final CZP population PK model also showed that the model provided a good description of the data; the observed data descriptors (the solid black line and the dashed black lines) lay within or very close to the model-predicted 95% confidence intervals (Figure 3). The very narrow model-predicted 95% confidence intervals (shaded areas) for the antibody-negative subjects (left-hand side of Figure 3) were due to the large number of subjects in this category, and consequently, the model was very precise. Correspondingly, the paucity of patients with CZP antibody-positive concentrations (6.4% of patients) is why the model-

predicted 95% confidence intervals were broader on the right-hand side of Figure 3.

## Discussion

The population PK model for CZP that has been built using the data from the 2157 CD patients has a simple structural form, which reflects the semisparseness of the PK data available, with little data during the absorption phase. The aim of the analysis was to determine which, if any, of the available covariates influence the disposition of CZP in CD patients; influential covariates may potentially be used to optimize CZP therapy, as discussed by Ordás et al.<sup>2</sup> The final model, with the included influence of CZP antibody-positive concentrations and covariates, describes the present data well, as evidenced by various forms of model evaluation including the VPC (Figure 3). The model contained what could be termed a nuisance parameter, the baseline. This parameter was necessary, as the assay for measuring CZP concentrations is not specific. Predose CZP concentrations can arise in 2 ways: either as a result of residual drug levels from a previous treatment with another anti-TNF immunoglobulin drug product or because there were endogenous antibodies directed against TNF. In most cases, the latter reason was the most likely, particularly where the baseline levels were low, just above the LLOQ. The assay used to measure CZP concentrations has the potential to cross-react with other IgG anti-TNF drugs, including; infliximab, adalimumab, and golimumab, but may not cross-react with etanercept, which has a different structure. The majority of ELISA assays that have been used to quantify plasma concentrations of other anti-TNF drugs have similar cross-reactivity characteristics. Interference of other anti-TNF drugs was controlled during the dosing period by the clinical study protocols, which prohibited the administration of other anti-TNF products during the conduct of the study and that these drugs have half-lives of 2 weeks or less.

The largest covariate influence found was the presence of CZP antibody-positive concentrations on CL/F (6% of the total data set). The presence or absence of CZP antibody-positive concentrations was included in the model in a binary fashion (yes/no), but led to an estimated increase in CL/F of 400% (population estimate of CL/F = 0.685 L/day in normal subjects and 2.74 L/day in subjects with CZP antibody-positive concentrations). A more accurate way to characterize the relationship between CL/F and CZP antibody-positive concentrations would have been to include the actual concentration values of the CZP antibody-positive concentrations, including evaluating whether different patterns exist, for example, transient elevations with limited effect on plasma exposure, or single time-point reductions in CZP



**Figure 3.** The VPC for the final certolizumab population PK model for ATB –ve (left) and ATB +ve (right) subjects, for continuous time (top) and time after dose (bottom). The solid black line is the median of the observed data; the dashed black lines are the limits between which 95% of the observed data are found. The gray-shaded area around the observed median and the gray-shaded areas around the observed 95% limits are the respective model-predicted 90% confidence intervals. VPC, visual predictive check; PK, pharmacokinetics; ATB –ve, antibody negative; ATB +ve, antibody positive.

exposure, with detectable antidrug antibodies that return to normal at a subsequent sampling time. This was not attempted because the assay for detecting the CZP antibodies was insufficiently sensitive and often the concentrations of CZP were seen to be decreasing before the actual of CZP antibody-positive concentrations could be detected. Thus, although using CZP antibody presence in a binary fashion is less interesting in a purist modeling setting, from the perspective of optimizing therapy for CD patients, it is appealing in its simplicity. In patients where CZP antibody-positive concentrations are detected, discontinuation of therapy could be considered, particularly if clinical response has been lost.

The covariate selected to describe body size was BSA. Body size was not a priori used with either fixed or estimated allometric coefficients, as it is well known that patients with Crohn's disease are often underweight because of the symptoms of the disease (nausea, diarrhea). Power relationships with body size were tested during the covariate model-building process but were inferior to the linear relationships that were retained in the final model. However, although BSA might have had the most statistically significant influence, obviously BSA, BMI, and WT are all very highly correlated, and thus in clinical practice, any measure of body size could probably be used. BSA influenced both CL/F and V/F in a linear

fashion, and both parameters increased with increasing BSA, which is in keeping with the relationships reported for infliximab.<sup>4</sup> The reason for the proportional increase in CL/F and V/F with size could be because larger subjects have a larger blood volume.

Of the remaining covariate influences detected, the influence of albumin concentrations on CZP CL/F was apparent and nonlinear in form; a higher CL/F of CZP was observed in patients with low albumin levels. These observations were consistent with the relationship reported for infliximab clearance and albumin<sup>4,15</sup> in ulcerative colitis and CD. In patients with active CD, lower plasma albumin concentrations have been extensively reported in the literature<sup>2,14,15</sup> and hypothesized to be due to the leakage of protein into the gastrointestinal track.<sup>2</sup> However, there is also some evidence that albumin production in the liver is reduced under highly inflammatory conditions<sup>16</sup> and may not only contribute to the reduced concentrations, but also to the nonlinear relationship with CZP CL/F.

CZP is a pegylated Fab' fragment that is thought to be primarily cleared by degradation into peptides and amino acids by proteolysis and is not dependent on FcRn protection, unlike a whole IgG such as infliximab.<sup>15</sup> However, in patients with active disease with low albumin, clearance of CZP is accelerated and most likely due to gut leakiness, as hypothesized for albumin, rather than any downregulation of FcRn activity, as suggested for infliximab.<sup>15</sup>

Normal serum albumin concentrations typically range between 35 g/L and 50 g/L. The characterized nonlinear relationship showed a steep decline for albumin concentrations that were below 41 g/L and was relatively flat for higher albumin concentrations, which is in keeping with the mechanism that a low albumin concentration is a marker for increased loss of CZP via the gut wall.

CRP is a marker for inflammatory activity and therefore, high CRP concentrations may, analogous to albumin, reflect decreased gut wall integrity. The influence of CRP on CZP CL/F was that CL/F increased with increasing CRP concentrations. This is in keeping with what has been found by Magro et al for infliximab,<sup>17</sup> where a high inflammatory burden at the start of therapy was correlated with a worse response, which by inference could be due to lower infliximab concentrations. Interestingly, Magro et al reported that the mean baseline concentration of CRP in CD patients who exhibited a sustained response was 9.6 mg/L, whereas it was 26.2 mg/L in patients who had a primary nonresponse. In the present analysis, the estimated cutoff, the point at which CZP CL/F increased much more slowly, was at a CRP concentration of 8 mg/L. However, the influence of CRP on drug concentrations and ultimately response to therapy is far from clear. Reinisch et al found that high baseline concentrations of CRP increased the likelihood of maintaining remission.<sup>18</sup> It may be possible that CRP

concentrations could have contradictory effects on drug concentrations and response to therapy. More work needs to be done to fully elucidate the influence of CRP on both the PK and pharmacodynamics (PD) of TNF- $\alpha$  inhibitors before it can be considered for use in optimizing TNF- $\alpha$  inhibitor therapy.

A minor effect of race was found on CZP V/F for black, Asian, and Japanese CD patients. However, with the exception of the Japanese (n = 89), the number of patients in the different race categories was small, and so this finding must be viewed very cautiously. In the absence of a defined PK/PD relationship for CZP, it can be hypothesized that response is related to overall exposure. As such, the 25% lower value for V/F found in Japanese patients will only alter the shape of the concentration-versus-time curve without affecting overall exposure and thus should not have any implication for treatment success or failure.

Interpretation of the importance of the covariates found in the present analysis is crucially dependent on the characterization of the PK/PD relationship, which can then relate changes in concentration to response outcome. Initial work to look at the effect of the plasma concentrations of CZP on endoscopic outcomes of patients with CD has been published by Colombel et al,<sup>9</sup> who found that endoscopic response and remission were associated with higher plasma concentrations of CZP in 89 patients with moderate to severe ileocolonic CD.

In conclusion, a population PK model has been developed for CZP that contains a number of covariate influences, the largest of which is the presence of antibodies to CZP that cause a 400% increase in CZP CL/F. The clinical utility of the influential covariates that have been identified in the present analysis has to be studied further.

## Declaration of Competing Interests

Janet R. Wade and Christian Laveille were paid consultants to UCB. Gerry Parker, Gordana Kosutic, and Ruth Oliver are employees of UCB. Brian G. Feagen and William J. Sandborn are clinical advisers to UCB.

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