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Modeling and Simulation of Abatacept Exposure and Interleukin-6 Response in Support of Recommended Doses for Rheumatoid Arthritis

Amit Roy, PhD, Diane R. Mould, PhD, Xiao-Feng Wang, PhD, Lee Tay, PhD, Ralph Raymond, and Marc Pfister, MD, FCP

Abatacept is a recombinant soluble fusion protein that inhibits the CD80/CD86:CD28 costimulatory signal required for T cell activation and has demonstrated efficacy in the treatment of rheumatoid arthritis. The objectives of this analysis were to provide support for a body weight–tiered dosing regimen approximating 10 mg/kg by (1) quantifying the effect of body weight on exposure and (2) characterizing the relationship between exposure and serum interleukin (IL)–6 concentration. The abatacept exposure and exposure–response models were developed with 2148 abatacept serum concentrations (from 388 subjects) and 1894 IL-6 serum concentrations (from 799 subjects), respectively, followed by simulation with these models to address the above objectives. Abatacept exposure was characterized by a linear 2-compartmental model, in which clearance was linearly related to body weight. The IL-6 response was characterized by an indirect-response model, in which the IL-6 production rate increased with baseline C-reactive protein

levels. Model-based simulations demonstrated that body weight–tiered dosing was desirable to ensure consistent steady-state abatacept trough concentrations across a range of body weights; doses approximating 10 mg/kg (500, 750, 1000 mg for subjects weighing <60, 60–100, and >100 kg, respectively) provided consistent exposure across the body weight groups. In addition, doses >10 mg/kg did not result in further increases in IL-6 suppression. These modeling and simulation results indicate that the body weight–tiered abatacept therapeutic doses approximating 10 mg/kg will ensure consistent abatacept exposure and optimal IL-6 suppression.

Keywords: Population pharmacokinetics; exposure response; abatacept; rheumatoid arthritis; IL-6

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The concept of model-based drug development, first proposed by Sheiner,¹ has been identified by the US Food and Drug Administration and the

European Medicines Agency as a key opportunity for improving the efficiency of drug development.^{2,3} The model-based approach has particular advantages in the selection and justification of dosing regimens.⁴ We have applied this approach to evaluate dosing regimens of abatacept in rheumatoid arthritis (RA) patients.

Abatacept is a recombinant soluble fusion protein that is the first in a class of agents that selectively modulate the CD80/CD86:CD28 costimulatory signal required for T cell activation. Abatacept consists of the extracellular domain of human cytotoxic T lymphocyte–associated antigen-4 (CTLA-4) and a fragment (hinge, CH2, and CH3 domains) of the Fc domain

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of human immunoglobulin G1 (IgG1), which has been modified to prevent complement fixation and antibody-dependent cellular cytotoxicity. It binds to CD80 and CD86 on antigen-presenting cells, thereby preventing their binding to the costimulatory molecule CD28 on T cells and inhibiting T cell activation.⁵

In RA, antigen-activated T cells orchestrate an inflammatory response by stimulating synovial macrophages and fibroblasts to produce interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α , which, in turn, activate more synovial fibroblasts, as well as osteoclasts, chondrocytes, and B cells.⁶ Abatacept has previously been reported to reduce serum levels of IL-6 and TNF- α ,^{7,8} both of which have been implicated as key players in the pathogenesis of RA.

The efficacy of abatacept in adult patients with moderate to severe active RA, who have had an inadequate response to 1 or more disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), or to anti-TNF therapy has been demonstrated in several phase II and III trials, as both monotherapy⁹ and in combination with other DMARDs.¹⁰⁻¹⁴ In particular, abatacept was shown to inhibit radiographic progression,¹² improve physical function, and provide significant improvements in the signs and symptoms of RA and health-related quality of life, relative to placebo.^{12,13}

The exposure of abatacept, like many other biologic agents, is expected to be dependent on body weight.¹⁵ Noncompartmental analysis of abatacept serum concentrations indicates that clearance increases as body weight increases. The objective of this modeling and simulation analysis was to provide support for the recommended body weight-tiered intravenous (IV) abatacept dosage by (1) quantifying the effect of body weight on exposure and (2) characterizing the exposure-response relationship for IL-6.

IL-6 was selected as a biomarker because serum levels are reduced in abatacept-treated RA patients,^{7,8} and overproduction of IL-6 has been implicated in RA disease pathology.¹⁶ This role in disease pathology is supported by the observation that therapeutic agents targeting IL-6 or its receptor can be clinically active in RA.^{17,18} Furthermore, serum IL-6 levels are elevated in patients with RA and are closely correlated with levels of the acute-phase reactant C-reactive protein (CRP), a general marker of inflammation.¹⁹ In fact, IL-6 is the chief stimulator of acute-phase proteins and is believed to be essential for the production of CRP.^{20,21} Therefore, abatacept-mediated reductions in IL-6 levels are expected to

lead to improvements in RA disease activity and reductions in overall inflammatory status.

METHODS

The abatacept serum exposure and exposure-IL-6 response models were developed with data collected from 3 phase II trials (A, B, and C), and 3 phase III trials (D, E, and F). This section presents brief descriptions of these clinical trials, the analytical methods, the exposure and exposure-IL-6 response data sets and model development, and the simulations in support of the recommended abatacept dosing regimen.

Clinical Trials

Phase II. Study A was a multicenter, randomized, double-blind, placebo-controlled monotherapy trial of RA patients receiving abatacept without other DMARDs. Abatacept was given at a dose of 0.5, 2.0, or 10.0 mg/kg and was administered by IV infusion over 1 hour on days 1, 15, 29, and 57. Serum samples for abatacept concentration were taken from each subject (approximately 7 and 25 samples from each sparsely and intensively sampled subject, respectively), and sampling was continued through day 169 of the study. Studies B and C were multicenter, randomized, double-blind, placebo-controlled studies. In study B, MTX was given in combination with abatacept or placebo; in study C, etanercept was given in combination with abatacept or placebo. Abatacept was administered by IV infusion over 30 minutes on days 1, 15, and 30, as well as every 4 weeks thereafter for 12 months at a dose of 2 or 10 mg/kg in study B and at 2 mg/kg in study C. Serum samples for abatacept concentration assessment were collected on day 60 at the end of infusion, at 4 hours after the start of infusion, and weekly thereafter until day 90.

Phase III. All 3 phase III trials (D, E, and F) were multicenter, randomized, double-blind, placebo-controlled studies in patients with RA. Abatacept or placebo was given in combination with MTX (study D) or DMARDs (studies E and F). For all 3 trials, abatacept was given by IV infusion over 30 minutes on days 1, 15, and 29, as well as every 4 weeks thereafter for the duration of the study, at a fixed dose according to body weight range (500 mg for subjects weighing <60 kg, 750 mg for subjects weighing 60-100 kg, and 1000 mg for subjects weighing >100 kg).

In studies D and E, trough serum samples were collected prior to administration of abatacept on all dosing days. Additional samples were collected based on a sparse sampling schedule over the dosing interval beginning on day 85 and ending on day 113. In study F, only trough samples were collected before dosing on days 1, 29, 85, 169, and 281. An additional 30-minute (end-of-infusion) sample was also taken on day 85.

All phase II and III trials were conducted and monitored by the Bristol-Myers Squibb Department of Global Clinical Research. All studies were approved by an institutional review board (IRB) or independent ethics committee (IEC) and were carried out in accordance with the ethical principles of the Declaration of Helsinki. A list of IRBs and IECs for these trials is provided in Appendix A (available online).

Analytical Methods

Abatacept was quantified in human serum samples using a validated enzyme-linked immunosorbent assay (ELISA) method with a range of reliable response from 1 to 30 ng/mL, as well as a lower limit of quantitation (LLOQ) of 1 ng/mL. The between- and within-run variability was less than $\pm 8.9\%$, based on the results of the analytical quality control (QC) samples. The mean observed concentrations of these analytical QC samples deviated less than $\pm 7.5\%$ from the nominal values. IL-6 was quantified in human serum using a commercially available ELISA method.⁸

Data Sets

Exposure data sets. All subjects for whom serum abatacept concentrations were available were included in the analysis of exposure. The combined exposure data set included 2148 measurements of abatacept serum concentrations from 388 subjects (238 subjects from phase II and 150 subjects from Phase III) and consisted of model-building and internal and external validation data sets. The model-building and internal validation data sets were created from the phase II data, comprising 8 subjects from study A, 164 subjects from study B, and 66 subjects from study C. Eighty percent ($n = 190$) of the phase II subjects were randomly selected for the model-building data set, and the remaining 20% ($n = 48$) of the phase II subjects were used as the internal model validation data set. The external validation data set consisted of 150 subjects, 50 from each of the 3 phase III studies. The phase II and III data sets were

combined to obtain the parameter estimates of the final exposure model.

The following baseline demographics and other covariates were included in the exposure analysis data sets: age, gender, body weight, laboratory parameters indicative of hepatic and renal status (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and serum creatinine), nominal abatacept dose, and related comedications, including MTX, DMARDs, corticosteroids, and anti-TNF blocking agents. Summary statistics of the demographic and other covariate variables for the exposure data sets are provided in Table I.

Exposure–IL-6 data set. The exposure–IL-6 response model was developed with data from subjects in the phase II and III studies in whom serum IL-6 measurements were available. All subjects randomized to receive placebo were included, but subjects randomized to receive abatacept were included only if abatacept concentration measurements and dose records were available. The data set contained 1894 IL-6 observations from 779 subjects, of whom 454 had received placebo and 325 had received abatacept. The following baseline covariates were included in this data set (in addition to those included in the exposure data set): CRP, rheumatoid factor (RF), sIL-2R, and TNF- α .

Model Development

The abatacept exposure and exposure–IL-6 response models were both developed using NONMEM (Version V, Level 1.1)²² for nonlinear mixed-effects (population) modeling. The NONMEM models were compiled and executed using Compaq Digital Visual Fortran (Version 6.6) and installed on a Pentium IV processor PC running under Microsoft Windows XP. Population models include a structural model specifying the functional relationship between the independent and dependent variables in the model, an interindividual variability (IIV) model specifying the distribution of individual parameter values, and a residual error model describing the distribution of differences between model predictions and observations. In addition, these models may include covariate models that explain a portion of the variability in individual parameter values.

Exposure model. The base exposure model consisted of a linear 2-compartment structural model with a constant rate of input (representing IV infusion), which was parameterized in terms of clearance (CL), central compartment volume of distribution (V₁),

Table I Baseline Demographics and Covariate Characteristics for the Exposure Data Sets

Covariate	Model-Building Data Set (n = 190) ^a	Internal Validation Data Set (n = 48) ^a	External Validation Data Set (n = 150) ^a	Combined Data Set (n = 388) ^a
Age, y (SD)	53.5 (11.6)	53.4 (13.5)	53.2 (12.2)	53.4 (12.0)
Weight, kg (SD)	78.9 (20.5)	81.3 (21.3)	76.5 (21.4)	78.3 (21.0)
ALT, U/L (SD)	19.9 (10.0)	22.3 (15.6)	20.0 (11.3)	20.3 (11.3)
AST, U/L (SD)	20.7 (8.0)	21.1 (7.8)	21.0 (9.5)	20.9 (8.5)
CREAT, mg/dL (SD)	1.0 (0.2)	1.0 (0.2)	0.7 (0.2)	0.9 (0.2)
Swollen joints, n (SD)	20.2 (9.2)	19.7 (7.5)	22.1 (9.6)	26.7 (12.5)
Tender joints, n (SD)	28.6 (12.0)	29.9 (12.7)	31.5 (13.2)	29.6 (12.5)
Disease duration, y (SD)	10.3 (9.3)	12.0 (11.2)	10.5 (8.3)	10.6 (9.2)
Female, n (%)	134 (70.5)	35 (72.9)	109 (72.7)	278 (71.7)
Caucasian, n (%)	170 (89.5)	44 (91.7)	139 (92.7)	353 (91.0)
<i>Concomitant medications</i>				
DMARDs, n (%)	184 (96.8)	48 (100)	145 (96.7)	377 (97.2)
MTX, n (%)	130 (68.4)	34 (70.8)	92 (61.3)	256 (66.0)
NSAID, n (%)	163 (85.8)	38 (79.2)	115 (76.7)	316 (81.4)
Corticosteroids, n (%)	59 (31.1)	12 (25.0)	43 (28.7)	114 (29.4)
Anti-TNF, n (%)	52 (27.4)	14 (29.2)	7 (4.7)	73 (18.8)
<i>Baseline biomarker levels^b</i>				
CRP, mg/L (SD)				30.5 (30)
sIL-2R, pg/mL (SD)				1555 (770)
RF, IU/L (SD)				232 (341)
TNF- α , pg/mL (SD)				50.7 (112)

SD, standard deviation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CREAT, creatinine; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; TNF, tumor necrosis factor; CRP, C-reactive protein; sIL-2R, soluble interleukin-2 receptor; RF, rheumatoid factor.

a. n varies for some covariates.

b. Baseline biomarkers were assessed as covariates only for the exposure-IL-6 response model.

peripheral compartment volume of distribution (V2), and intercompartment clearance (Q). A 2-compartmental model was selected on the basis of earlier preliminary analysis and the visually evident biexponential decline in abatacept serum concentrations. The IIV in model parameters was described by lognormal distributions, which constrained the parameters to have positive values for all subjects. Alternative IIV models were tested, by allowing for correlations between individual exposure parameter values and also by allowing only a subset of the exposure parameters to have IIV.

The value of parameter P_k for individual i is given by

$$P_{k,i} = P_{k,AVG} \exp(\eta_{k,i}),$$

$$\eta_{k,i} \sim N(0, \omega_k^2),$$

where $P_{k,AVG}$ is the average value of parameter P_k (corresponding to a model-based estimate of the geometric mean), and $\eta_{k,i}$ is a realization from a normally distributed random variable with zero mean and variance ω_k^2 .

The residual error models tested included additive, proportional, and combined (both additive and proportional) models. In addition, separate error models were evaluated for subjects with intensive versus sparse sampling of abatacept concentrations to account for the possibility that the monitoring of the intensively sampled subjects may have been more rigorous, leading to more accurate data collection.

The combined residual error model is specified by

$$y_{ij} = \hat{y}_{ij} (1 + \epsilon_{PROP,ij}) + \epsilon_{ADD,ij},$$

$$\epsilon_{PROP} \sim N(0, \sigma_{PROP}^2), \epsilon_{ADD} \sim N(0, \sigma_{ADD}^2),$$

where y_{ij} is the j th abatacept serum concentration in subject i , \hat{y}_{ij} is the corresponding model-predicted concentration, and $\epsilon_{PROP,ij}$ and $\epsilon_{ADD,ij}$ are realizations of independent normally distributed random variables, with zero mean and variances of σ_{PROP}^2 and σ_{ADD}^2 , respectively.

The effect of covariates on exposure model parameters was screened by graphical analyses and tested with covariate models that described the relationship between the value of the covariate and the

average value of the exposure parameter. Covariate model testing was restricted to physiologically reasonable covariate relationships. Model building followed a standard forward addition/backward elimination procedure, based on the likelihood ratio test, which is based on the property that the ratio of the NONMEM objective function values (OFV) of nested models is asymptotically chi-square distributed, with degrees of freedom equal to the difference in the number of model parameters. A significance level of 1% was employed for the forward addition and 0.1% for the backward elimination in testing for covariates for exposure models, to adjust for the multiple comparisons being made during this evaluation.

Other considerations for covariate acceptance included reduction in IIV and improvement in goodness-of-fit plots, such as plots of population predictions versus observed concentrations, and weighted residual versus population predictions. In addition, all covariate factors accepted into the model must have been shown to have clinical relevance (greater than $\pm 20\%$ effect on parameter value). Model qualification was conducted with internal and external validation data sets, as well as with the combined data set by checking the predictive performance of the model.

Exposure–IL-6 response model. The structural model used to describe serum IL-6 concentrations was an indirect-response model,²³ in which serum IL-6 concentration is given by

$$\frac{dC_{IL-6,i}}{dt} = K_{syn,i} - K_{deg,i}C_{IL-6,i},$$

where $C_{IL-6,i}$ is the serum IL-6 concentration in subject i at time t , $K_{syn,i}$ is the zero-order production rate of IL-6, and $K_{deg,i}$ is the first-order coefficient for the degradation of IL-6. The effect of abatacept on IL-6 was described by examining several alternative drug effect models, in which abatacept serum concentrations had an effect on K_{syn} or K_{deg} or both. Concentrations of abatacept and IL-6 were described simultaneously with the pharmacokinetic parameters being fixed to the estimated values of the exposure model. Linear and hyperbolic (E_{max}) effect relationships were examined. The IIV model for the exposure–IL-6 response model parameters is similar to that for the exposure parameters, as described above. The residual error was described by a combined error model. The model was evaluated through nonparametric bootstrap and visual predictive check.

Model-Based Simulations

The exposure model was used to simulate steady-state trough concentrations ($C_{min,ss}$) of abatacept for each of the subjects in the phase III trials for whom abatacept concentration data were available. Trough concentration is believed to be the most relevant measure of exposure based on the results of an in vitro assay of the inhibition of T cell activation, which suggested that abatacept concentrations of 3 to 10 $\mu\text{g/mL}$ are needed for maximal effect.²⁴ Adequacy of the recommended body weight–tiered doses was evaluated by comparing the distributions of $C_{min,ss}$ for each of the fixed abatacept doses of 500, 750, and 1000 mg.

The exposure–IL-6 response model was used to simulate inhibition of serum IL-6 concentration for the studied doses, as well as for higher doses (20 and 50 mg/kg) that have not been studied in any clinical trial. Adequacy of abatacept doses approximating 10 mg/kg was assessed by quantifying the incremental inhibition of serum IL-6 that would be expected at higher doses.

RESULTS

The development of the abatacept exposure and exposure–IL-6 response models are described below, followed by simulation results that support body weight–tiered therapeutic doses for patients with RA. Key steps in the development of the models are presented in Table II.

Exposure Model

Abatacept serum concentrations were described by a linear 2-compartmental model formulated in terms of IIV in CL, V1 and V2, and a combined residual error model. An IIV model (in which all parameters other than Q were correlated) was selected as the best IIV model based on the OFV and reduction in the variances of random effect parameters. An assessment of alternative residual error models determined that the goodness of fit improved when separate residual error models were employed for subjects with intensive and sparse abatacept concentration samples. The additive component of the residual error was negligible for the intensively sampled subjects but not for the subjects with sparse samples. The estimates of the proportional error were similar for both intensively and sparsely sampled subjects. Therefore, the residual error model selected had a common proportional error for all subjects but included an additive error for the sparsely sampled subjects.

Table II Key Model Development Steps

Model Number	Model Description	OFV	Minimization	Comments
Exposure model				
1	Two-compartment model, full-block IIV on CL, V1 and V2, and combined residual error	3495.48	Successful	Initial stable model
2	Same as #1, but with combined and proportional residual error for sparse and rich samples, respectively	3473.16	Successful	Removing additive error for rich samples improved fit and decreased OFV by 22.3
3	Base model: Same as #2, but no covariance between CL and V2	3477.90	Successful	Removing covariance between CL and V2 decreased OFV by 4.74
4	Base model, with CL~WT and V1~WT	3437.79	Successful	Adding WT as covariate on CL and V1 decreased OFV by 40.1 ($P < .01$)
5	Final model: Base model, with CL~WT	3439.23	Successful	Removing WT on V1 only decreased OFV by 1.44 ($P < .001$)
IL-6 exposure-response model				
6	Indirect-response model with drug effect on K_{syn} and IIV on K_{syn} , K_{deg} , EC_{50} , and E_{max}	24 425.44	Terminated	Initial model with drug effect on K_{syn} terminated
7	Same as #6, but with no IIV on K_{syn} and EC_{50}	23 658.27	Successful	Model with drug effect on K_{syn} converged after removing IIV on K_{syn} and EC_{50}
8	Indirect-response model with drug effect on K_{deg} and IIV on K_{syn} , K_{deg} , EC_{50} , and E_{max}	23599.37	Terminated	Initial model with drug effect on K_{deg} terminated
9	Base model: same as #8, but with no IIV on EC_{50}	23 630.43	Successful	Removing IIV on EC_{50} provided model with lowest OFV that converged successfully
10	Base model, with $K_{syn} \sim$ CRP + IL-2	23 412.60	Successful	Adding CRP and IL-2 as covariates on K_{syn} decreased OFV by 217.8 ($P < .01$)
11	Base model, with $K_{syn} \sim$ CRP	23 413.57	Successful	Removing effect of IL-2 on K_{syn} increased OFV by only 0.97 ($P < .001$)

OFV, objective function value; IIV, interindividual variability; CL, total clearance of intravenous administered doses; V1, distribution volume of the central compartment; V2, distribution volume of the peripheral compartment; WT, body weight of an individual subject; K_{syn} , synthesis rate constant; K_{deg} , degradation rate constant; EC_{50} , concentration at which half the maximal effect is achieved; E_{max} , maximal effect; CRP, C-reactive protein; IL, interleukin.

The relationship between model parameters and the following covariates was examined: age, gender, race, body weight, ALT, AST, serum creatinine, disease status (swollen and tender joints), and comedications (MTX, DMARDs, corticosteroids, and anti-TNF blocking agents). The only statistically significant and clinically relevant covariate effect on a model parameter identified was the effect of body weight on clearance, which was described by the following relationship:

$$CL_{AVG,i} = CL_0 + CL_1 \frac{BW_i}{BW_{REF}}$$

where the $CL_{AVG,i}$ is the theoretical population average value clearance for all subjects with a body weight identical to the body weight of subject i . BW_i denotes the body weight of subject i , BW_{REF} is the reference body weight of 78.9 kg, and CL_0 and CL_1 are estimated fixed-effect model parameters. Inclusion of the relationship explained approximately 20% of the IIV in clearance.

Predictive check evaluations of the model with the internal, external, and combined data sets indicated that the final model is adequate to describe the exposure of abatacept. In the internal predictive check evaluation, 15 of 154 (9.7%) observations fell outside the 95% confidence interval (CI). In the external

Table III Final Exposure Model Parameter Estimates: Combined Data Set

Parameter, ^a Units	Estimate	Standard Error (% RSE)
CL ₀ , L/day	0.333	0.0326 (9.79)
V1 _{AVG} , L	3.22	0.0789 (2.45)
Q _{AVG} , L/day	0.525	0.0596 (11.4)
V2 _{AVG} , L/day	4.68	0.287 (6.13)
CL ₁ , L/day	0.210	0.0338 (16.1)
Interindividual random effects		
VAR(η_{CL})	0.293	0.0106 (12.4)
VAR(η_{V1})	0.242	0.00988 (16.9)
VAR(η_{V2})	0.351	0.0422 (34.3)
COV($\eta_{CL};\eta_{V1}$)	0.712	0.00873 (17.3)
COV($\eta_{V1};\eta_{V2}$)	0.617	0.0118 (22.5)
Residual error		
VAR(ϵ_{PROP})	0.250	0.00589 (9.39)
VAR(ϵ_{ADD}), $\mu\text{g}/\text{mL}$	1.32	1.03 (59.5)

RSE, relative standard error ($100 \times$ standard error/estimate); CL, total clearance of intravenous administered doses; V1, distribution volume of the central compartment; AVG, average; Q, intercompartmental clearance; V2, distribution volume of the peripheral compartment; VAR, variance; η , interindividual variability in model parameters; COV, covariance; ϵ , intrasubject error model parameter; PROP, proportional; ADD, additive.

a. Estimated interindividual random effect parameters are shown as standard deviation for variances and correlation for covariances.

predictive check evaluation, 87 of 1069 (8.1%) observations fell outside the 95% CI. Therefore, discrepancy between the nominal and observed percentage of observations outside the 95% CI is relatively small.

Improved fit of the model to the data was obtained by re-estimating the parameters in the final exposure model with all available data (combined exposure data set). The parameter estimates of the final model are presented in Table III. The estimated population average volume of distribution of abatacept at steady state (V_{ss} , estimated as the sum of the central and peripheral volumes of distribution) is 8.9 L. For a subject with a body weight of 80 kg (the approximate mean weight in the database), this equates to a V_{ss} of 0.11 L/kg. The estimated population average clearance of abatacept for a subject with a body weight of 80 kg (calculated from the covariate relationship for CL_{AVG}, in terms of CL₀ and CL₁) is 0.55 L/day, or approximately 0.29 mL/h/kg.

A predictive performance check evaluation of the trough concentrations is presented in Figure 1. The 25th percentile of observed trough serum concentration was in good agreement with the 25th percentile calculated from simulated data sets, whereas the simulated data tended to overpredict the 50th and 75th percentiles. However, the magnitude of the

overprediction was relatively modest (2-3 $\mu\text{g}/\text{mL}$, 5%-10%) and is not expected to be clinically meaningful as the deviations occur in subjects with high exposures, who are thereby less likely to lack clinical efficacy. Therefore, the final exposure model is considered to provide an adequate description of the exposure data.

Relationships between individual estimates of abatacept clearance and covariates in individual maximum a posteriori Bayesian estimates of clearance were obtained from the final model, with the combined exposure data set, to quantify the magnitude of the effect of these covariates as a means of examining their potential for clinical relevance. The magnitude of the effect on abatacept clearance of body weight, age, gender, and comedication is provided below.

Effect of body weight. The effect of body weight on clearance determined is shown in Figure 2. The pattern of the individual clearance estimates suggests that clearance tends to increase as body weight increases. Several alternative functional relationships were examined using the likelihood ratio test, and the linear relationship shown in Figure 2 was found to be supported by the data. The line showing the population average value of clearance for subjects with a given body weight represents the population geometric mean of the lognormal distribution of clearance as a function of weight.

Effect of comedication. The ratios of the geometric means of clearance of subjects on a given comedication relative to subjects not on comedication were 1.04 for MTX, 0.99 for nonsteroidal anti-inflammatory drugs (NSAIDs), 1.09 for corticosteroids, and 0.97 for the anti-TNF agents. The distribution of individual clearance estimates as a function of coadministered drug is shown in Figure 3A-D. The median values fall well within 20% of the population average. These plots confirm the model-building covariate analysis finding that coadministered drugs do not affect abatacept clearance.

Effect of age and gender. The distributions of individual estimates of clearance with respect to age are consistent with the finding of the model-development covariate analysis that age does not have a significant effect on clearance. The ratio of the geometric mean of clearance of women relative to men was 0.86, after accounting for the effect of body weight, a difference that is not expected to be clinically relevant. This ratio of geometric mean clearances is thought to be robust, given the large number of both female ($n = 278$) and male ($n = 110$) subjects.

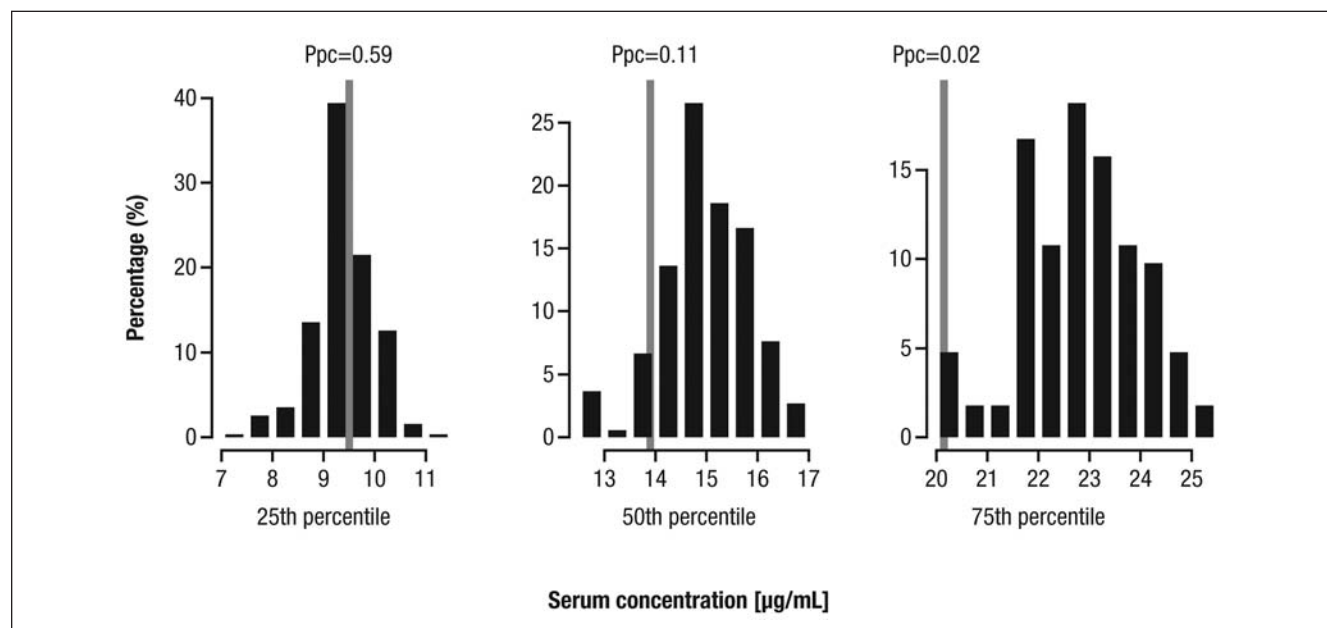


Figure 1. Predictive performance check for trough concentrations (dose = nominal 10 mg/kg). The 25th, 50th, and 75th percentiles of the observed trough concentration distributions for a nominal dose of 10 mg/kg are compared with the corresponding percentiles from 200 data sets simulated by the final exposure model. The Ppc value represents the proportion of a percentile statistic calculated from simulated data that is greater than the value of the percentile statistic calculated from the observed data. Ppc, proportion predictive check.

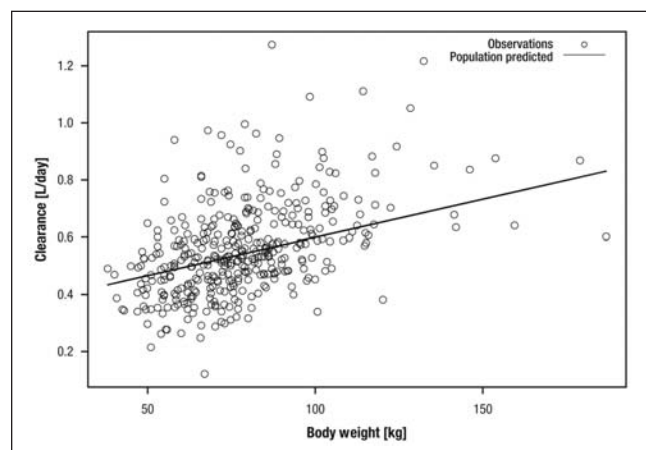


Figure 2. Clearance versus body weight. The symbols represent individual maximum a posteriori Bayesian estimates of clearance; the line represents the model-estimated relationship between body weight and population average clearance.

Simulation-Based Evaluation of Body Weight-Tiered Abatacept Doses

The body weight-tiered doses of abatacept were evaluated by examining the distributions of model-predicted steady-state trough serum concentrations

at each of the proposed doses of 500, 750, and 1000 mg employed in the phase III studies, for body weight ranges of <60 kg, 60 to 100 kg, and >100 kg, respectively.

A comparison of the distributions of model-predicted steady-state trough serum concentrations for each of the 150 subjects in the phase III data set is shown in Figure 4. Steady-state trough concentrations were predicted for subjects based on maximum a posteriori Bayesian individual exposure parameter estimates. The high degree of overlap in the predicted steady-state trough concentration distributions corroborates the conclusion that the proposed weight-tiered dose adjustment is appropriate.

Exposure-IL-6 Response Model

Interleukin-6 serum concentrations were adequately described by an indirect-response model given by

$$\frac{dC_{IL-6,i}}{dt} = K_{syn,i} - K_{deg,i} \left(1 + \frac{E_{max,i} C_{d,i}}{EC_{50,i} + C_{d,i}} \right) C_{IL-6,i},$$

the parameter estimates of which are presented in Table IV.

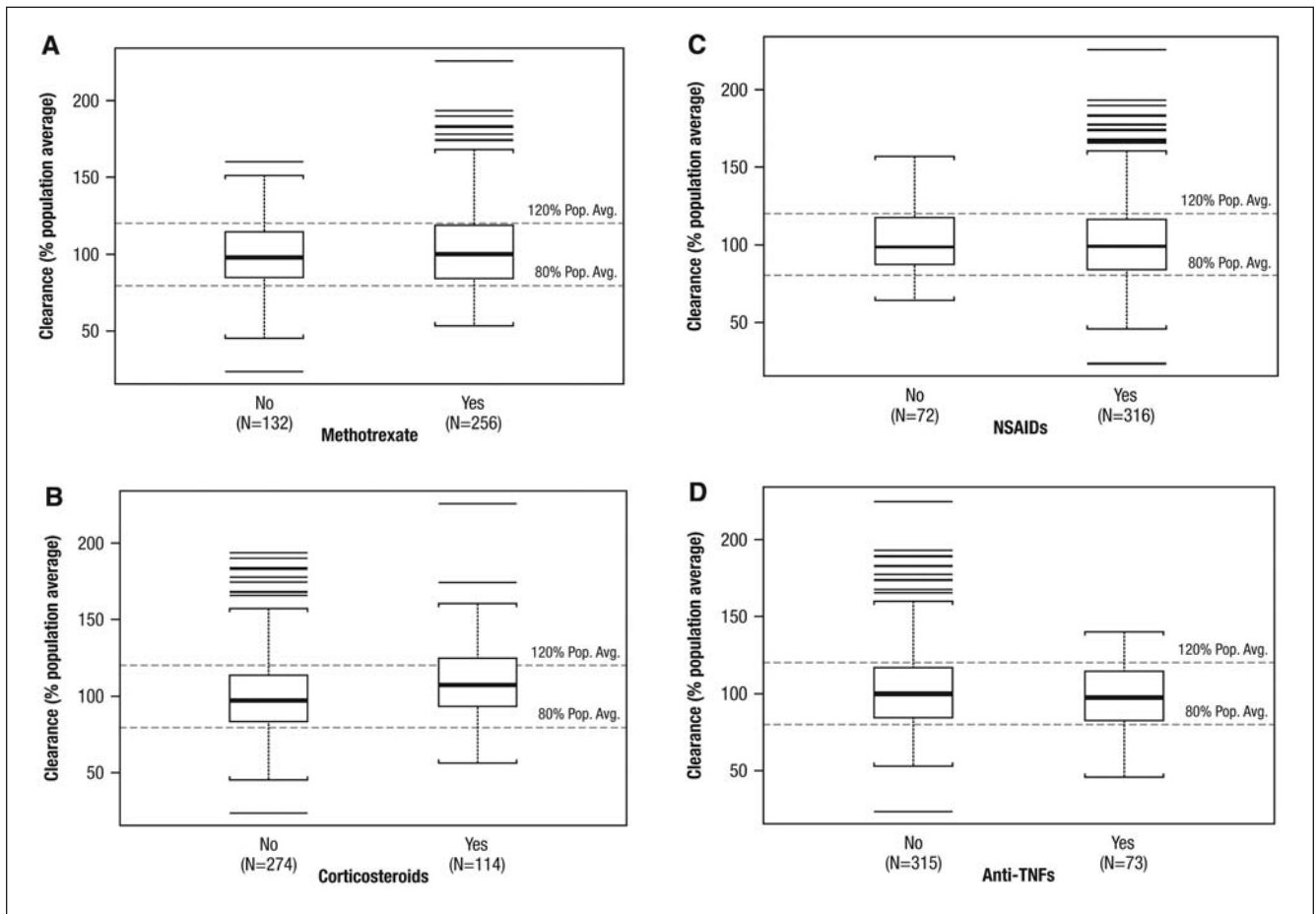


Figure 3. Distribution of individual clearance estimates as a function of coadministered (A) methotrexate, (B) corticosteroids, (C) nonsteroidal anti-inflammatory drugs, and (D) anti-tumor necrosis factor therapy. The lower and upper ends of the boxes represent the 25th and 75th percentiles of the distribution, the bold line represents the median, and the whiskers extend to the range of the data, or to 1.5 times the interquartile distance beyond the box, whichever is greater. Horizontal dotted lines show 80% and 120% of the Pop.Avg. NSAID, nonsteroidal anti-inflammatory drug; TNF, tumor necrosis factor; Pop.Avg, population average.

The covariate analysis examined the effect of age, swollen and tender joint counts, CRP, RF, sIL-2R, and TNF- α . The only significant covariate effect identified, other than abatacept concentration, was the effect of baseline CRP on $K_{syn,AVG}$, the population average synthesis rate of IL-6, given by

$$K_{syn,AVG} = K_{syn,0} \left(\frac{C_{CRP,0}}{C_{CRP,REF}} \right)^{K_{syn,1}}$$

where $K_{syn,AVG}$ is the population average value of K_{syn} , for a baseline CRP value of $C_{CRP,0}$. $C_{CRP,REF}$ is a reference CRP value of 21 mg/mL, and $K_{syn,0}$ and $K_{syn,1}$ are estimated fixed-effect parameters.

Simulation-Based Evaluation of IL-6 Levels Corresponding to Body Weight-Normalized Abatacept Dose

The effect of abatacept doses of 2, 10, 20, and 50 mg/kg on serum IL-6 concentrations was examined by simulation using the final exposure-IL-6 response model (Figure 5). The simulated median IL-6 serum concentration-time profiles show that steady state is reached by approximately 3 months and that the IL-6 levels for the 10-mg/kg dose were markedly lower than that for the 2-mg/kg dose. However, higher doses of 20 and 50 mg/kg did not result in further suppression of IL-6. Stochastic simulations were

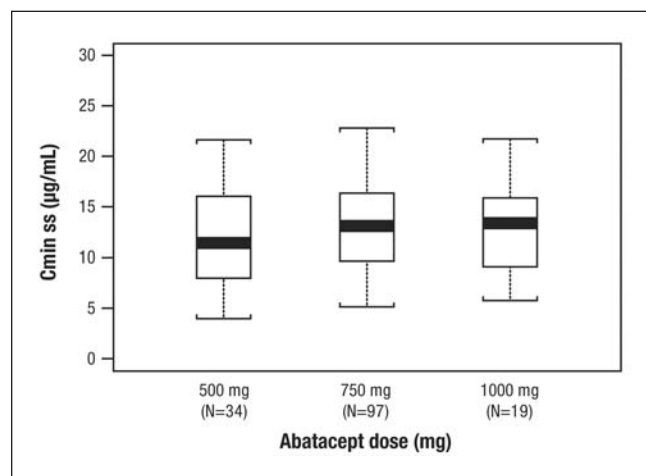


Figure 4. Distributions of predicted steady-state trough serum concentrations by dose group. The median and the 25th and 75th percentiles of the distribution are given by the bold horizontal line and edges of a box; the 5th and 95th percentiles are represented by the whiskers of a box.

conducted to assess day 90 serum IL-6 concentrations for the placebo and the 2-, 10-, and 20-mg/kg dose groups (Figure 6). One thousand replicates of approximately 200 subjects per dose group were generated, and box and whisker plots were used to depict the distribution of day 90 IL-6 levels. For the placebo group, the simulated median day 90 IL-6 concentration was 18.9 pg/mL, whereas for the 2-mg/kg dose group, it was 6.73 pg/mL. The 10- and 20-mg/kg dose groups had similar simulated median day 90 IL-6 concentrations of 5.99 and 5.96 pg/mL, respectively.

DISCUSSION

Results from this modeling and simulation analysis support a body weight–tiered abatacept dosing regimen for RA patients. These data demonstrate that abatacept doses of 500, 750, or 1000 mg every 4 weeks to RA patients weighing <60, 60 to 100, or >100 kg result in (a) steady-state abatacept trough concentrations that are similar across the body weight range in this patient population and (b) near-maximal reductions in IL-6 serum concentration levels, which is expected to correlate with maximal clinical efficacy.

Abatacept, a fully human soluble fusion protein, is a large protein (92 kDa); therefore, transfer across cell membranes to extravascular spaces is likely to be limited, owing to its size and hydrophilicity. The

Table IV Final Exposure–IL-6 Response Model Parameter Values

Parameter, Units	Parameter Value	95% Confidence Interval
Fixed effects		
$K_{syn,0}$, pg/mL/day	0.401	0.212-0.714
$K_{syn,1}$	0.61	0.535-0.695
K_{deg} , 1/day	0.0189	0.0108-0.0343
E_{max}	3.66	1.58-6.6
EC_{50} , µg/mL	11.3	1.91-56.4
Random effect parameters		
$SD(\eta_{K_{syn}})$	0.45	0.16-0.65
$SD(\eta_{K_{deg}})$	0.62	0.37-0.74
$SD(\eta_{EC_{max}})$	1.12	0.88-1.37
Residual error parameters		
$SD(\epsilon_{ADD})$	16.4	14.49-18.84

K_{syn} , synthesis rate constant; K_{deg} , degradation rate constant; E_{max} , maximal effect; EC_{50} , concentration at which half the maximal effect is achieved; SD, standard deviation; η , interindividual variability in model parameters; ϵ , intrasubject error model parameter; ADD, additive.

abatacept distribution volume of 8.9 L is consistent with the distribution of 6 to 9 L for other macromolecules of this size.²⁵ The V_{ss} of abatacept for a patient with a body weight of 80 kg is 0.11 L/kg.

The population average clearance of 0.55 L/day (0.29 mL/h/kg for an 80-kg patient) that was estimated in the present analysis is comparable with an average clearance of 0.22 mL/h/kg ($n = 14$; range, 0.13-0.47) determined by noncompartmental analysis.²⁶ The relationship between abatacept clearance and body weight was described by a linear covariate model, parameterized in terms of an intercept (CL_0) and a slope (CL_1). A subject weighing 40 kg would be expected to have a 19% lower clearance than the reference subject, whereas a subject weighing 160 kg would be expected to have a 35% higher clearance. Therefore, the effect of body weight is substantial and clinically relevant, making a body weight–tiered dosing regimen important to ensure similar exposures across the body weight range in the RA patient population. However, no dose adjustment is needed for gender or age, as no exposure model parameters were related to these covariates. Although it does not appear that race or laboratory parameters of hepatic and renal status have an effect on abatacept, the range of these variables in the exposure data set may not have been sufficiently wide to elucidate a relationship. The finding that abatacept clearance increases with body weight is also consistent with that of other protein therapeutics.²⁷ However,

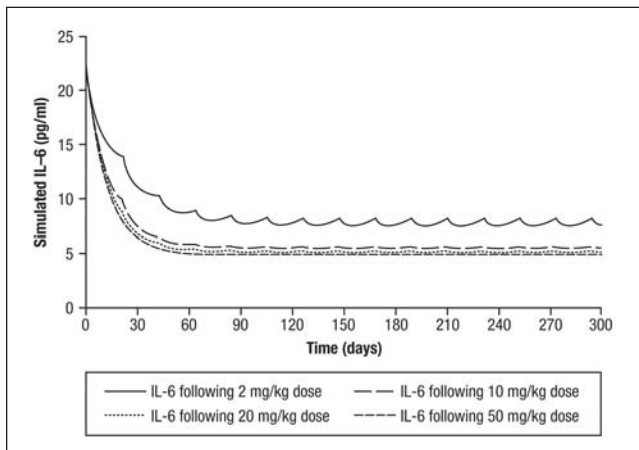


Figure 5. Simulated average serum interleukin-6 (IL-6) concentrations versus time, by abatacept dose. Simulated median IL-6 concentrations over time for 2 mg/kg abatacept (solid line), 10 mg/kg abatacept (long dashed line), 20 mg/kg abatacept (intermediate dashed line), and 50 mg/kg abatacept (short dashed line).

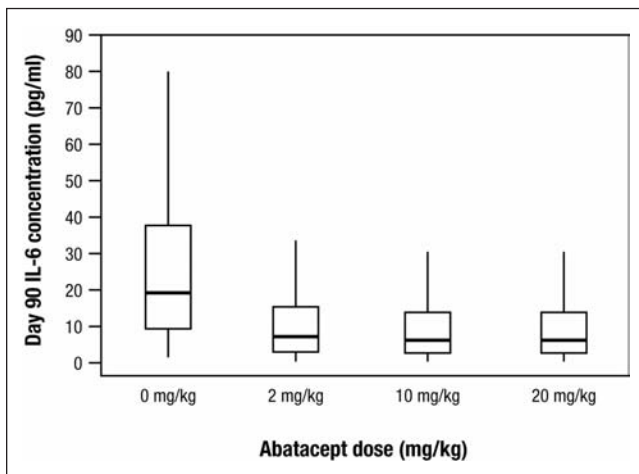


Figure 6. Simulated distributions of serum interleukin-6 (IL-6) concentrations on day 90, by abatacept dose. The median and the 25th and 75th percentiles of the distribution are given by the bold horizontal line and edges of a box; the 5th and 95th percentiles are represented by the whiskers of a box.

unlike many monoclonal antibodies, which exhibit nonlinear clearance,²⁵ abatacept clearance does not change with dose.

Abatacept is not thought to be cleared by cytochrome enzymes or mixed-function oxidases and would, therefore, not be expected to alter the exposure of other comedications. However, there may be potential mechanisms of interaction with concomitant

medications that could affect exposure to abatacept. For example, steroids alter macrophage cell trafficking^{28,29} and, therefore, could potentially alter the clearance of abatacept. All but 3 subjects in the present database received 1 or more concomitant medications. The largest effect on clearance among the comedications tested (MTX, NSAIDs, steroids, and anti-TNF blocking agents) was for corticosteroids, which resulted in a 9.9% increase in clearance. The magnitude of this change was not considered to be clinically relevant, and the results indicate that commonly coadministered drugs had very little impact on the exposure of abatacept. Therefore, no adjustment of abatacept dose would be required when abatacept is coadministered with MTX, corticosteroids, NSAIDs, or anti-TNF blocking agents.

The exposure–IL-6 response analysis characterized the suppression of serum IL-6 following treatment with abatacept. The observed serum IL-6 concentrations were described using an indirect-response model, in which the synthesis rate of IL-6 was positively correlated to baseline CRP, resulting in higher IL-6 serum concentrations. This relationship is physiologically reasonable as IL-6 is the primary stimulator of CRP²⁰; therefore, higher baseline CRP levels are indicative of a higher baseline IL-6 production rate.

Simulation with the exposure–IL-6 response model indicated an increase in IL-6 suppression with 10 mg/kg abatacept compared with 2 mg/kg, but increasing the dose beyond 10 mg/kg did not result in further decreases in IL-6 serum concentrations. It should be noted, however, that uncertainty in the exposure–response model was not considered in the simulation exercise. The decrease in IL-6 concentration for 10 mg/kg relative to 2 mg/kg mirrors the differences observed in clinical measures of disease activity with these 2 doses. In a double-blind, placebo-controlled phase IIb trial of patients with active RA,¹⁰ ACR 20 responses (20% improvement in the American College of Rheumatology score) were significantly greater in patients receiving 10 mg/kg abatacept ($n = 115$) compared with patients receiving placebo ($n = 119$) at 1 year (62.6% vs 36.1%, respectively, $P < .001$). However, no significant differences in ACR 20 responses were observed in the 2-mg/kg abatacept group ($n = 105$) relative to placebo. As the highest dose of abatacept studied in clinical trials with RA patients approximates the 10-mg/kg dose, ACR 20 responses for higher abatacept doses are not available. However, the exposure–IL-6 model prediction that suppression of IL-6 is asymptotically maximal for the 10-mg/kg dose (Figure 5)

suggests that higher doses would not offer further improvements of clinical efficacy.

In conclusion, the results of the exposure analysis model for abatacept demonstrate that abatacept can be administered to patients with RA, without concern that factors such as age, gender, and comediations may negatively affect treatment. The only clinically relevant covariate effect for exposure was the effect of body weight on clearance. The exposure–IL-6 response model suggests that increasing the abatacept dose beyond 10 mg/kg is not likely to result in additional clinical benefit and supports the recommended dosage of abatacept in RA patients. Based on these findings, a dose regimen approximating 10 mg/kg (500, 750, and 1000 mg for patients weighing <60, 60–100, and >100 kg, respectively) is recommended for this agent.

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