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Population Pharmacokinetics and Exposure-Response Relationship of Intravenous and Subcutaneous Abatacept in Patients With Rheumatoid Arthritis

Xiaohui Li, PhD*, Amit Roy, PhD, and Bindu Murthy, PharmD

Abstract

Abatacept population pharmacokinetics (PK) and exposure-response (E-R) models for selective efficacy end points were developed using phase 2 and 3 study data in patients with rheumatoid arthritis treated with abatacept (intravenous [IV] or subcutaneous [SC]), followed by simulations. Two efficacy end points were assessed in the E-R analyses: Disease Activity Score in 28 joints (DAS28) and American College of Rheumatology response criteria for 20/50/70% improvement (ACR20/50/70). The analyses were performed with data from 11 clinical studies for the population PK analysis and from 3 clinical studies for the E-R analyses (DAS28 and ACR20/50/70). The PK of abatacept were time invariant and can be described by a linear 2-compartment model with first-order elimination and with zero-order IV infusion or first-order absorption for SC abatacept. Baseline body weight was the only clinically meaningful covariate; that is, abatacept clearance and volume of central compartment increased with increasing baseline body weight. Steady-state trough concentration (C_{minss}) of abatacept was identified as the best exposure predictor of DAS28 response compared with other exposure measures. In addition, the E-R relationship was the same for IV and SC abatacept. Similar results were confirmed in the ACR20/50/70 E-R analyses. Efficacy responses increased with increasing C_{minss} and a near-maximal response was associated with $C_{minss} \geq 10$ μg/mL. The model-based analyses confirmed that the weight-tiered ~10 mg/kg IV and fixed 125 mg SC abatacept dosing regimens are comparable and achieved plateau responses, by delivering $C_{minss} \geq 10$ μg/mL in RA patients across all body weights.

Keywords

abatacept, biologics, pharmacodynamics, population pharmacokinetics, rheumatology

Abatacept, a selective costimulation modulator, is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T lymphocyte (T cell)-associated antigen 4 linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1.[1] Antigen-specific T cells are believed to play a central role in the pathogenesis of autoimmune diseases. Abatacept inhibits T-cell activation by binding to CD80 and CD86 on antigen-presenting cells, and thereby blocking interaction with the costimulatory molecule CD28 on the T cell.[1] The interaction with CD28 provides a costimulatory signal that is necessary for full activation of T cells, which are found in the synovium of patients with rheumatoid arthritis (RA) and are implicated in the pathogenesis of the disease. By inhibiting full T-cell activation, abatacept also affects the downstream inflammatory cascade.

Abatacept is approved for the treatment of adult patients with moderate-to-severe active RA in several countries, including the United States and European Union, with the weight-tiered intravenous (IV) dosing regimen and the fixed subcutaneous (SC) dosing regimen approved for use in this population.[2] Fixed SC abatacept (125 mg once weekly [QW]) has been shown to have equivalent efficacy and comparable safety to the weight-tiered IV abatacept (~10 mg/kg: ie, 500, 750, 1000 mg for patients weighing <60, 60 to 100, and >100 kg, respectively) every 4 weeks (Q4W) in adult patients with moderate to severe active RA.[3,4] In addition, IV and SC abatacept are approved for the treatment of pediatric patients with moderate to severe active polyarticular juvenile idiopathic arthritis and adults with active psoriatic arthritis.[2]

The pharmacokinetics (PK) of abatacept following IV administration have been characterized by a linear 2-compartment model, in which clearance was linearly related to body weight.[5] The relationship between exposure and serum interleukin-6 concentration was characterized by an indirect response model,

Bristol-Myers Squibb, Princeton, NJ, USA

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Corresponding Author:
Bindu Murthy, PharmD, Bristol-Myers Squibb, Mailstop E.2143, P.O. Box 4000, Princeton, NJ 08543-4000
Email: Bindu.murthy@bms.com

*Affiliation at time of study

in which the interleukin-6 production rate increased with baseline C-reactive protein levels. Model-based simulations demonstrated that body weight–tiered abatacept IV dosing (~10 mg/kg Q4W)[2] provided consistent abatacept exposure (steady-state trough concentration [C_{minss}]) across the body weight groups. Doses >10 mg/kg did not result in further increases in interleukin-6 suppression. IV abatacept PK were also characterized in the Japanese population using a linear 2-compartment model, in which body weight and the empirically calculated glomerular filtration rate (cGFR) were significant covariates for clearance.[6] In a study investigating the relationship between abatacept exposure and efficacy (Disease Activity Score in 28 joints [DAS28]) in patients with RA following SC or IV administration, abatacept C_{minss} was the best exposure predictor of DAS28 response.[7]

The objectives of the analyses reported here, performed using combined data from phase 2/3 studies with IV or SC abatacept administration, were (1) to characterize the population PK of abatacept and to investigate and quantify potential relationships between covariates and abatacept PK parameters in patients with RA; and (2) to characterize the efficacy exposure-response (E-R) relationship between abatacept exposure and selective efficacy end points in patients with RA, for both IV and SC abatacept. The efficacy end points included in the 2 E-R analyses were DAS28 up to 6 months and American College of Rheumatology response criteria for 20/50/70% improvement (ACR20/50/70) at 6 months after initiation of treatment, respectively. This report describes the development, evaluation, and application of the population PK and E-R models, including the assessment of the potential effect of covariates on abatacept PK and efficacy. Where approved, the justifications for the abatacept fixed SC dose regimen is largely based on the population PK analyses and E-R results reported here.

Methods

Data and Study Populations

All study protocols, their amendments, and informed consent documentation for studies included in the population PK and E-R analyses (Table S1) were reviewed and approved by institutional review boards (Table S2), and were conducted in accordance with the codes and guidelines set forth in the Declaration of Helsinki, Good Clinical Practice, and local regulations.

The population PK model was developed with data from 2244 patients enrolled in 11 clinical trials (4 phase 2, 7 phase 3) in patients with RA. Among these studies, IV abatacept was administered in 6 studies, SC abatacept was administered in 4 studies, and 1 study (ACQUIRE [Abatacept Comparison of Subcutaneous Versus Intravenous in Inadequate Responders to Methotrexate]) investigated both IV and SC abatacept. Doses of abatacept across all studies ranged from 0.5 to 10 mg/kg Q4W for IV administration and 75 to 200 mg QW for SC administration. Abatacept serum concentrations were measured by a validated enzyme-linked immunosorbent assay, with a lower limit of quantification of 1.0 ng/mL. Abatacept SC concentrations in the population PK data set were flagged and excluded from the analysis if missing information on the dose or sample could not be imputed. Samples with duplicate assay results at the same collection time and those below the lower limit of quantification were also excluded from the analyses. The SC abatacept formulation used in the phase 2 trial was modified, with different pH for use in the phase 3 trials to improve product stability.

The E-R models for DAS28 and ACR20/50/70 were developed using data from 3 trials (1 phase 2, 2 phase 3) in patients with RA. Of these, 2 studies used IV abatacept, and 1 study (ACQUIRE) included both SC and IV abatacept treatments. The DAS28 and ACR E-R analyses included all patients with compliance with Good Clinical Practice regulations for whom measures of abatacept exposure (steady-state peak, trough, and time-average concentration; C_{maxss}, C_{minss}, and C_{avgss}, respectively) were available from the population PK analysis. Specifically, the E-R analysis data set included 14 902 observations (at Days 15, 29, 57, 85, 113, 141, and 169) in 1958 patients for DAS28 and 1893 observations in 1893 patients for ACR20/50/70.

The population PK and efficacy E-R analyses were performed using the NONMEM computer program (Version VI, level 2.0; Icon Development Solutions, Hanover, Maryland), compiled using GNU FORTRAN version 77, installed on a Linux platform. Diagnostic graphics, exploratory analyses, and post-processing of NONMEM output was performed using the S-Plus software (Version 7.0.0 for Linux; Insightful, Seattle, Washington) on a Linux platform and R (Version 3.2.1).

Population Pharmacokinetics Analysis

The population PK model of abatacept was characterized by a nonlinear mixed-effects model that was developed in 3 stages. First, a stable and parsimonious base model was developed to describe abatacept serum concentration–time data in patients with RA without consideration of covariate effects. Base model development consisted of determining 3 component models: a structural PK model, an interindividual (IIV) model, and a residual variability model. SC bioavailability included in the population PK model was the absolute bioavailability for SC administration of abatacept. As absolute bioavailability is bound between zero

and one, the absolute bioavailability is modeled using the inverse logit function, as shown in the following equation:

$$F_{Abs,i} = \frac{1}{1 + \exp(-F_{TV,i})}$$

$$F_{TV,i} = F_{TV} + F_{IIV,i}$$

where $F_{Abs,i}$ is the individual absolute bioavailability, F_{TV} is the model-estimated typical value for bioavailability prior to transformation, and F_{IIV} is the model-estimated IIV for bioavailability prior to transformation. The shape of the F_{Abs} distribution versus $F_{TV} + F_{IIV}$ (logit of F_{Abs}) is presented in Figure S1.

The abatacept concentration-time profiles from clinical studies showed that the time to maximum concentration (T_{max}) for SC abatacept was ~4 days and the terminal half-life was ~14 days for both IV and SC abatacept.[2] This indicates that the kinetics of absorption are 4-fold faster than the kinetics of elimination, and therefore justifies the constraint of rate of absorption (KA) > rate of elimination (K_{el}) in the abatacept population PK model to prevent flip-flop of parameter estimates and to ensure that the rate of absorption is always higher than the rate of elimination. Individual KA values are expressed as the sum of the individual estimated relative rates of absorption and the individual rate of elimination as shown in the following equation:

$$KA_i = KA_{TV} \times \exp(KA_{IIV,i}) + K_{el,i}$$

$$K_{el,i} = \frac{CL_i}{VC_i}$$

where KA_i is the individual absolute rate of absorption, KA_{TV} is the model-estimated typical value for the relative rate of absorption, and KA_{IIV} is the model-estimated IIV for relative rate of absorption. $K_{el,i}$ is the individual rate of elimination, which is the quotient of the individual clearance (CL_i) and central volume of distribution (VC_i).

A full model was developed by assessing the effects of previously identified covariates on population PK model parameters in a univariate analysis. The following covariates at baseline were investigated: body weight; age; sex; race; coadministration of nonsteroidal anti-inflammatory drugs (NSAIDs), methotrexate, and corticosteroids; albumin; total bilirubin; cGFR; disease duration; swollen joint count; tender joint count; and SC formulation (phase 2 formulation or phase 3 formulation). Covariate effects were estimated relative to the following reference values of covariates: 50-year-old male, body weight of 70 kg, baseline albumin of 4.0 mg/dL, cGFR of 90 mL/min/1.73 m^2, swollen joint count of 16, not taking concomitant NSAIDs, and treated with phase 3 SC formulation of abatacept. These reference values represent the approximate median values of the continuous covariates in the data set or the mode of categorical covariates, except for sex where male is used as the reference.

The final model was developed by backward elimination of covariates from the full model until all remaining covariates were significant at a 0.1% level (likelihood ratio test). After elimination of the statistically insignificant covariates, the clinical relevance of covariates that were retained in the final model was assessed. For both continuous and categorical covariates, covariates that resulted in <−20% or +25% change in point estimates and 95% confidence intervals (CIs) that fall within 80% to 125% of the reference value were determined to be not clinically relevant.

Model evaluation was conducted by visual and quantitative predictive performance check methods for the approved IV (~10 mg/kg Q4W) and SC (125 mg QW) abatacept dosing regimens,[2] respectively, at steady state. The visual predictive check compared observed and model-predicted serum abatacept concentrations in patients with RA at actual sampling times after previous dose at approximate steady state.

Efficacy E-R Analysis: 28-Joint Disease Activity Score

An E-R analysis was conducted to study the relationship between abatacept exposure and DAS28 response up to month 6 after initiation of treatment. A nonlinear mixed-effects inhibitory maximum drug effect model with respect to exposure and time (E_{max} model) was developed. In this model, the maximal reduction in DAS28 is a function of exposure, whereas the time to reach 50% reduction in DAS28 score is independent of exposure. Alternative measures of exposure (C_{maxss}, C_{minss}, and C_{avgss}) of abatacept were tested to identify the best measure of exposure for prediction of DAS28 response. Development of the DAS28 E-R model was conducted in 3 stages.

First, a base model was developed to determine the existence and functional form of the relationship between abatacept exposure and DAS28 response; this mixed-effects inhibitory E_{max} model describes the DAS28 score for the ith subject at time t_{ij} as:

$$DAS28_{ij} = E_{0,i} - \frac{E_{max,i}\, t_{ij}}{T_{50,i} + t_{ij}} + \varepsilon_{ij}$$

where

$$E_{max,i} = E_{pbo,i} + E_{aba,i}$$

$$E_{aba,i} = f(C_{aba,i}) = \frac{E_{aba}\, C_{minss}}{EC_{50} + C_{minss}}$$

with model parameters corresponding to the *i*th subject's DAS28 score at baseline ($E_{0,i}$), maximal reduction in DAS28 score ($E_{max,i}$), and the time at which 50% of the maximal reduction in DAS28 score is achieved ($T_{50,i}$). The maximal reduction in DAS28 score comprises the reduction due to placebo effect ($E_{pbo,i}$) (ie, the effect other than the abatacept treatment effect) and the reduction due to the abatacept effect ($E_{aba,i}$), where $E_{aba,i}$ is a function of abatacept exposure; the functions tested were linear, log-linear, and E_{max}.

A full model was developed by incorporating the effects of all statistically significant prespecified covariate-parameter relationships, which were examined for the following covariates at baseline: age, sex, race, body weight, DAS28 score at baseline (E_0), and treatment type (IV or SC). The reference subject for the purpose of the covariate analysis was defined as the following: 50-year-old male, body weight 60 to 100 kg, white, baseline DAS28 score of 6, IV route of administration, no concomitant corticosteroid use, and treatment (SC abatacept). The full model was constructed using a univariate analysis with all covariates that were significant at a 0.1% level when added individually to the base model.

The final model was developed from the full model by backward elimination of covariate-parameter relationships that were statistically insignificant at a 0.1% level.

Model evaluation was conducted by visual and quantitative predictive performance check methods for the approved IV (~10 mg/kg Q4W), SC (125 mg QW) abatacept dosing regimens, and placebo, respectively, up to 6 months.

Efficacy E-R Analysis: American College of Rheumatology 20/50/70 Response Criteria

The relationship between the probability of achieving cumulative ACR20/50/70 response criteria at 6 months and abatacept C_{minss} was described by an ordered categorical proportional-odds logistic regression model and included assessments of the potential modulatory effect of covariates on this E-R relationship. The selection of C_{minss} as the exposure measure in this E-R analysis was based on pharmacologic rationale as well as the knowledge from the E-R analysis for DAS28 (see Results for Efficacy E-R Analysis: 28-Joint Disease Activity Score) that C_{minss} was the appropriate measure of exposure for efficacy in adult patients with RA who received IV or SC abatacept. The C_{minss} exposure was estimated by the population PK analysis (as described in Population PK Analysis).

The E-R model of ACR20/50/70 was developed using data from all patients with available C_{minss} from the studies described above, with a C_{minss} value of zero imputed for patients who received placebo. The probability of achieving cumulative ACR20/50/70 responses as a function of C_{minss} was assessed using an ordered categorical proportional-odds model, in which the log-odds (logit) of achieving an ACR20, ACR50, and ACR70 response was given by a series of expressions, each describing the probability that the response achieved was at least as much as the level specified (ie, $P[Y \geq 20\%] = P[\text{ACR20}]$):

$$\textbf{logit}\ P_{ACR20,i} = \log\left(\frac{P_{ACR20,i}}{1 - P_{ACR20,i}}\right) = \beta_{ACR20} + f(C_{minss,i}) + \boldsymbol{\beta}^T \boldsymbol{X}_i$$

$$\textbf{logit}\ P_{ACR50,i} = \log\left(\frac{P_{ACR50,i}}{1 - P_{ACR50,i}}\right) = \beta_{ACR20} + \beta_{ACR50} + f(C_{minss,i}) + \boldsymbol{\beta}^T \boldsymbol{X}_i$$

$$\textbf{logit}\ P_{ACR70,i} = \log\left(\frac{P_{ACR70,i}}{1 - P_{ACR70,i}}\right) = \beta_{ACR20} + \beta_{ACR50} + \beta_{ACR70} + f(C_{minss,i}) + \boldsymbol{\beta}^T \boldsymbol{X}_i$$

respectively, where $P_{ACR20,i}$, $P_{ACR50,i}$, and $P_{ACR70,i}$ are the probabilities that subject *i* will achieve ACR20, ACR50, and ACR70 responses, respectively. β_{ACR20} is the log-odds that a reference subject will achieve an ACR20 response on placebo treatment, β_{ACR50} is the log-odds that a subject will achieve an ACR50 response relative to an ACR20 response, and β_{ACR70} is the log-odds that a subject will achieve an ACR70 response relative to an ACR50 response. The $f(C_{minss})$ term represents a function describing the effect of C_{minss} on the log-odds of achieving a response for a reference subject; and $\boldsymbol{\beta}$ is a parameter vector representing the effect of the predictor variable vector $\boldsymbol{X}_i$ on the log-odds of achieving a response, where $\boldsymbol{X}_i$ consists of the covariate values of subject *i*. Model parameters were estimated by maximum likelihood.

The model was developed in 2 stages: (1) a base model was developed to characterize the relationship between the probability of achieving an ACR20/50/70 response and C_{minss}, without consideration of the potentially modulatory effect of covariate predictor variables; and (2) a full model was developed by incorporating all of the following covariates into the base model: age, sex, body weight category (<60 kg, 60 to 100 kg, or >100 kg), race, baseline DAS28 score, route of administration, concomitant corticosteroid use, and study. Body weight was not characterized as a continuous variable but as a categorical covariate, using the 3 body weight groups in the recommended IV abatacept

dosing regimen: <60 kg, 60 to 100 kg, and >100 kg. The ACR model was developed subsequently to the DAS28 model to address questions from health authorities. Backward elimination to obtain a parsimonious model (final model) was not performed as the model was not intended to be used for simulation.

In the full model, a categorical covariate was considered significant if the 95%CI of the odds ratio (OR) did not include 1. For a continuous covariate, if the 95%CI of the covariate effect at the 5th or 95th percentile of the covariates did not include 1, then the covariate effect at these extremes of the covariate distribution was considered significantly different compared with the reference value of the covariate.

Results

Population PK Analysis

Following exclusions for missing information on dose or sample, a total of 11 628/13 610 (85.4%) samples were included in the population PK analysis. Of these, a further 1246 samples were excluded because they were below the lower limit of quantification, leaving 10 382/11 628 (89.3%) samples included in the data set. The baseline demographic, laboratory, and disease status variables in the population PK data set are summarized in Table S3.

Abatacept PK were characterized by a linear 2-compartment population PK model with zero-order IV infusion or first-order absorption of SC abatacept and first-order elimination with a combined residual error model, with random effect on bioavailability (F), KA, CL, VC, inter-compartmental clearance (Q), and volume of distribution for peripheral compartment (VP), and a full block correlation matrix of the random effects of CL, VC, Q, and VP. Parameter estimates of the structural part of the final population PK model are provided in Table 1A.

The covariate effects on the typical values of structural model parameters were described by the following expressions:

$$CL_{TV,i} = CL_{TV,ref}\left(\frac{BWT_i}{BWT_{ref}}\right)^{CL_{BWT}}\left(\frac{AGE_i}{AGE_{ref}}\right)^{CL_{AGE}}$$
$$\left(\frac{ALB_i}{ALB_{ref}}\right)^{CL_{ALB}}\left(\frac{CGFR_i}{CGFR_{ref}}\right)^{CL_{cGFR}}\left(\frac{SWOL_i+1}{SWOL_{ref}+1}\right)^{CL_{SWOL}}$$
$$\times \exp(SEX_i \cdot CL_{SEX} + NSAID_i \cdot CL_{NSAID})$$
$$\int VC_{TV,i} = VC_{TV,ref}\left(\frac{BWT_i}{BWT_{ref}}\right)^{VC_{BWT}}$$
$$Q_{TV} = Q_{TV,ref}$$
$$VP_{TV,i} = VP_{TV,ref}\left(\frac{BWT_i}{BWT_{ref}}\right)^{VP_{BWT}}$$
$$F_{TV,i} = F_{TV,ref} + FORM_i \cdot F_{FORM}$$

Table 1. Parameter Estimates for (A) the Structural Part of Final PPK Model for Abatacept and (B) the Covariates of the Full PPK Model

Parameter (Units)[a]	Estimate[b]	Standard Error (RSE%)[c]	95% Confidence Interval[d]
A: Structural part of final PPK model			
Fixed effects			
$CL_{TV,ref}$ (L/h)	0.0204	0.000454 (2.23)	0.0195, 0.0213
$VC_{TV,ref}$ (L)	3.27	0.0555 (1.70)	3.16, 3.38
$Q_{TV,ref}$ (L/h)	0.0265	0.00246 (9.28)	0.0217, 0.0313
$VP_{TV,ref}$ (L)	4.26	0.191 (4.48)	3.89, 4.63
KA_{TV} (1/h)	0.00305	0.000827 (27.1)	0.00143, 0.00467
SC $F_{TV,ref}$ (–)[e]	1.42	0.111 (7.82)	1.20, 1.64
Random effects			
ZCL (–)	0.0991 (0.315)	0.00688 (6.94)	0.0856, 0.113
ZVC (–)	0.0632 (0.251)	0.00938 (14.8)	0.0448, 0.0816
ZQ (–)	0.429 (0.655)	0.104 (24.2)	0.225, 0.633
ZVP (–)	0.377 (0.614)	0.0641 (17.0)	0.251, 0.503
ZKA (–)	1.63 (1.28)	0.541 (33.2)	0.570, 2.69
ZF (–)	0.710 (0.843)	0.115 (16.2)	0.485, 0.935
ZCL:ZVC	0.0412 (0.521)	0.0108 (26.2)	0.0200, 0.0624
ZCL:ZQ	0.0952 (0.462)	0.0272 (28.6)	0.0419, 0.149
ZVC:ZQ	0.0407 (0.247)	0.0350 (86.0)	–0.0279, 0.109
ZCL:ZVP	0.0910 (0.471)	0.0197 (21.6)	0.0524, 0.130
ZVC:ZVP	0.0675 (0.437)	0.0218 (32.3)	0.0248, 0.110
ZQ:ZVP	0.280 (0.696)	0.0752 (26.9)	0.133, 0.427
Residual error			
θ_{PROP} (–)	0.215	0.00719 (3.34)	0.201, 0.229
θ_{ADD} (μg/mL)	0.341	0.116 (34.0)	0.114, 0.568
B: Covariates of full PPK model			
CL ~ BWT	0.651	0.0320 (4.92)	0.588, 0.714
VC ~ BWT	0.452	0.0579 (12.8)	0.339, 0.565
VP ~ BWT	0.457	0.0922 (20.2)	0.276, 0.638
F ~ FORM	−1.16	0.152 (13.1)	−1.46, −0.862
CL ~ cGFR	0.162	0.0255 (15.7)	0.112, 0.212
Cl ~ SEX	−0.0722	0.0169 (23.4)	−0.105, −0.0391
CL ~ ALB	−0.687	0.0862 (12.5)	−0.856, −0.518
CL ~ NSAID	0.0640	0.0169 (26.4)	0.0309, 0.0971
CL ~ SWOL	0.0965	0.0116 (12.0)	0.0738, 0.119
CL ~ AGE	−0.186	0.0272 (14.6)	−0.239, −0.133
CL ~ MTX	−0.0405	0.0247 (61.0)	−0.0889, 0.00791

ALB, albumin; BWT, baseline body weight; cGFR, calculated glomerular filtration rate; CL, total clearance; F, bioavailability; FORM, formulation; *KA*, rate of first-order absorption; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drug; PPK, population pharmacokinetic; Q, intercompartmental clearance; RSE, relative standard error; SC, subcutaneous; SWOL, swollen joint count; TV, typical value; VC, volume of distribution (central compartment); VP, volume of distribution (peripheral compartment); Z, variance estimate; θ_{ADD}, standard deviation of the additive of the residual error; θ_{PROP}, standard deviation of the proportional of the residual error.

[a]The reference values for the covariates are BWT_{ref} = 70 kg, AGE_{ref} = 50 years, ALB_{ref} = 4.0 mg/dL, $cGFR_{ref}$ = 90 mL/min/1.73 m^2, $SWOL_{ref}$ = 16, SEX_{ref} = male, $NSAID_{ref}$ = no, $FORM_{ref}$ = phase 3 SC formulation.

[b]Random-effects parameter estimates are shown as variance (standard deviation) for diagonal elements (ZP) and covariance (correlation) for off-diagonal elements (ZP_1;ZP_2).

[c]RSE% is the relative standard error (standard error as a percentage of estimate).

[d]Confidence intervals of random-effects parameters are for variance or covariance. The results are not from bootstrap runs due to the run time for a single model run >15 hours.

[e]$F_{TV,ref}$ is the absolute bioavailability, $F_{Absolute} = 1/(1+\exp(-F_{TV}-F_{IIV})$, at the reference value $F_{Absolute}$ = 80.5%.

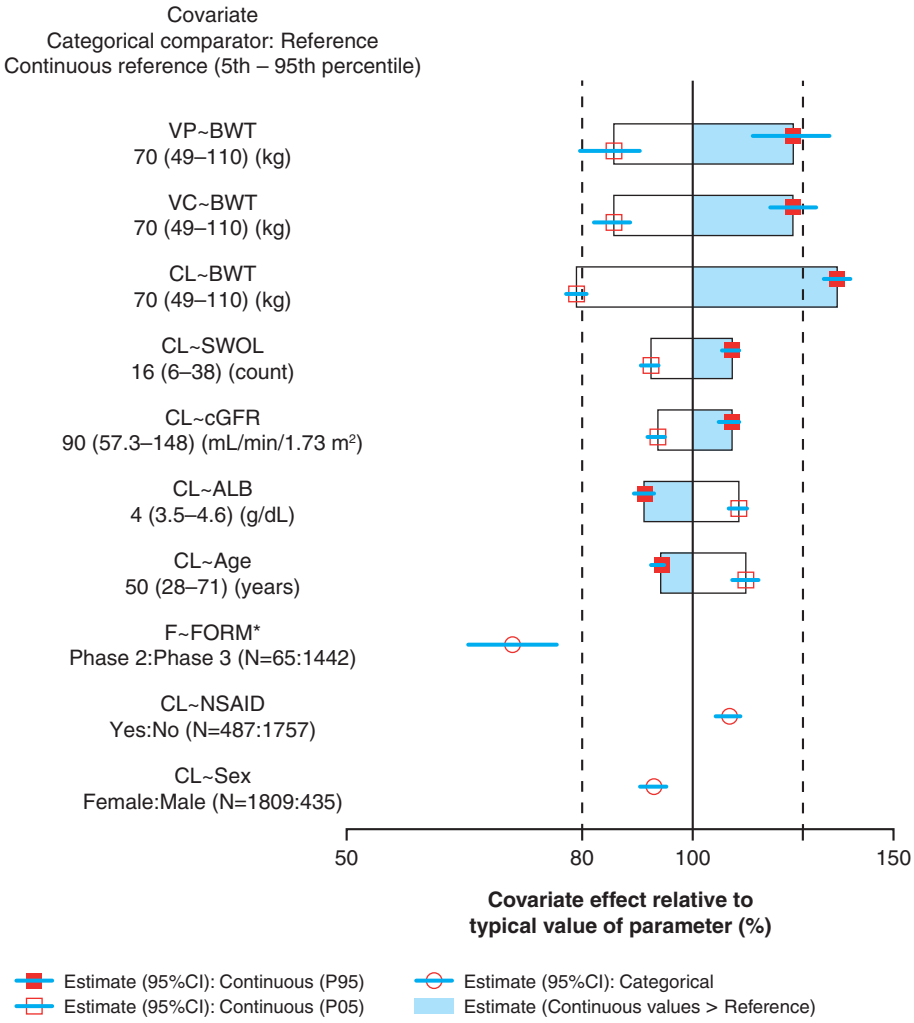

Figure 1. Covariate effects plot based on final population PK model. Reference subject is male, BWT = 70 kg, age = 50 years, cGFR = 90 mL/min/1.73 m^2, albumin = 4.0 mg/dL, swollen joint count = 16, not taking NSAIDs, and using phase 3 SC formulation. Parameter estimate in reference subject is considered as 100% (vertical solid line), and dashed vertical lines are at 80% and 125% of this value (no-effect interval). ALB, albumin; BWT, baseline body weight; cGFR, calculated glomerular filtration rate; CI, confidence interval; CL, total clearance; F, bioavailability; FORM, formulation; NSAID, nonsteroidal anti-inflammatory drug; PK, pharmacokinetic; SC, subcutaneous; SWOL, swollen joint count; VC, volume of distribution (central compartment); VP, volume of distribution (peripheral compartment). *For the SC formulation, if patient had both phase 2 and 3 formulations, the patient was counted once for phase 2 and once for phase 3.

where $P_{TV,ref}$ is the typical value of a PK parameter (P) for a reference (*ref*) subject and *FORM* is the SC formulation (phase 2 SC or phase 3 SC formulation). The reference subject is a 50-year-old man, body weight of 70 kg, baseline albumin of 4.0 mg/dL, cGFR of 90 mL/min/1.73m^2, swollen joint count of 16, not taking concomitant NSAIDs, and treated with phase 3 SC formulation of abatacept.

The parameter estimates for the covariate influence on the PK of abatacept are presented in Table 1B. Analysis of covariate effects revealed that *CL* increased with body weight, cGFR, and swollen joint count; decreased with age and albumin levels; was lower in females than males and higher in patients treated with concomitant NSAIDs (Figure 1). Furthermore, *VC* and *VP* increased with body weight, and *F* was lower for the phase 2 SC formulation of abatacept. The difference between the phase 2 and 3 SC formulations was observed in a clinical study in which both SC formulations were studied (Bristol-Myers Squibb, data on file). Among these covariate effects, only the body weight effect was clinically relevant. As shown in Figure 1, the 95%CI of the effect of baseline body weight on *CL* exceeded the 80% to 125% no-effect interval, and thus was considered as clinically relevant. The 95%CI for the effect of body weight on *VC* and *VP* also exceeded 125%, suggesting clinical relevance. In contrast, the other covariate effects were within the 80% to 125% no-effect interval, and thus were not considered clinically relevant.

Individual PK exposures for patients in the ACQUIRE study (the phase 3 study including both IV and SC abatacept treatments)[3] were simulated using the maximum a posteriori PK parameter estimates of each individual with the dosing per protocol. For both IV and SC dosing regimens, ~90% of patients achieved a C_{minss} of 10 μg/mL that was associated with the near-maximal efficacy response that was identified in the later E-R analysis. The simulated C_{minss} was summarized by body weight group (Figure S2) and showed that the C_{minss} for SC abatacept increased as body weight decreased but was similar across body weight groups (<60, 60 to 100, >100 kg) for IV abatacept. The C_{minss} for the highest body weight group with SC dosing was comparable with the C_{minss} for all 3 body weight groups with IV dosing (Figure S2).

Efficacy E-R Analysis: 28-Joint Disease Activity Score

There was a significant relationship demonstrated between exposure and efficacy response as measured by DAS28 score. The E-R analyses E_{max}-T_{max} model indicated that abatacept C_{minss} was the best measure of exposure for predicting the DAS28 response compared with C_{maxss} and C_{avgss} (Table S4). An E_{max} effect of C_{minss} on the maximal drug effect seems to be a better functional form of an exposure effect compared with a linear effect and a log-linear effect. Models A1205_5A3 and D1205_5A3 have the lowest OFVs of all the models by including an exposure effect on the time of the DAS28 response. However, both models have a conditional number exceeding 1000, indicating overparameterization; thus, they were not selected as the base model. Based on the results shown in Table S4, D1203_5A3 was selected as the base model, an E_{max}-T_{max} model with C_{minss} as the measure of exposure affecting only the magnitude of the DAS28 response, with a full block matrix IIV on E_0, $E_{max,aba}$ and T_{50}, with additive residual error.

The base model function is shown below:

$$DAS28\,(t) = E_0 - E_{max}\frac{t}{T_{50}+t}$$

$$E_{max} = E_{max,pbo} + \frac{E_{max,aba} \times C_{minss}}{EC_{50} + C_{minss}}$$

where $DAS28(t)$ is the DAS28 score at time t, E_0 is the baseline DAS28 score, E_{max} is maximum DAS28 response, $E_{\mathrm{max,pbo}}$ is the maximum DAS28 response due to placebo (ie, the non-abatacept intervention, occurring in both placebo and abatacept-treated patients), $E_{\mathrm{max,aba}}$ is the maximum DAS28 response due to abatacept, EC_{50} is the abatacept concentration needed to achieve half-maximum drug response, T_{50} is time to achieve half-maximum response, and C_{minss} is the model-predicted steady-state trough serum concentrations.

Table 2. Final E-R DAS28 Model Parameter Estimates

Name (Units)[a]	Estimate[b]	Standard Error (RSE%)[c]	95% Confidence Interval[d]
Fixed effects			
E_0 (–)	6.22	0.0201 (0.323)	6.18, 6.26
$E_{max,pbo}$ (–)	1.97	0.165 (8.38)	1.62, 2.27
T_{50} (day)	63.2	5.50 (8.70)	50.6, 72.9
$E_{max,aba}$ (–)	2.15	0.159 (7.39)	1.84, 2.45
EC_{50} (μg/mL)	6.82	1.69 (24.8)	3.76, 10.4
$E_{max,pbo}$ ~ E0	1.00	0.125 (12.5)	0.688, 1.17
$E_{max,aba}$ ~ AGE	−0.381	0.0871 (22.9)	−0.540, −0.212
Random effects			
ZEmax (–)	1.44 (1.20)	0.192 (13.3)	1.19, 1.97
ZE_0 (–)	0.423 (0.650)	0.0228 (5.39)	0.385, 0.477
ZT_{50} (–)	1.34 (1.16)	0.264 (19.7)	0.588, 1.64
ZE_0:ZT_{50}	0.571 (0.758)	0.0616 (10.8)	0.395, 0.647
Residual error			
θ_{ADD} (–)	0.360 (0.600)	0.00869 (2.41)	0.344, 0.377

DAS28, 28-joint Disease Activity Score; E_0, baseline DAS28 score; EC_{50}, concentration needed to achieve half of maximum drug response; $E_{max,pbo}$, maximum placebo DAS28 response; $E_{max,aba}$, maximum drug DAS28 response; E_{max}, maximum DAS28 response; E-R, exposure-response; IIV, intra-individual variability; RSE, relative standard error; T_{50}, time to achieve half of maximum response; Z, variance estimate; θ_{ADD}, standard deviation of the additive of the residual error.

[a]The reference values for the covariates are $E0_{IIV,ref} = 0$, $AGE_{ref} = 50$ years.

[b]Random-effects parameter estimates are shown as variance (standard deviation) for diagonal elements (ZP) and covariance (correlation) for off-diagonal elements (ZP_1;ZP_2).

[c]RSE% is the relative standard error (standard error as a percentage of estimate).

[d]Confidence intervals of random-effects parameters are for variance or covariance; all confidence intervals are from 500 bootstrap runs.

For the full model, with C_{minss} as the measure of exposure predicting the DAS28 response, treatment effect (IV vs SC) was not a significant covariate on any of the E-R parameters tested ($E_{max,pbo}$, $E_{max,aba}$, T_{50}, or EC_{50}). The final E-R model for DAS28 was an E_{max}-T_{max} model with C_{minss} as the measure of exposure, with an additive error, with random effect on $E0$, E_{max}, and T_{50}, with correlation between $E0$ and T_{50}. Parameter estimates of the final E-R model for DAS28 are shown in Table 2. The covariate analysis showed that the placebo response ($E_{max,pbo}$) increased with baseline DAS28 ($E0$) and drug response ($E_{max,aba}$) decreased with age. The covariate effects were modeled as the following:

$$E_{max,pbo_{TV,i}} = E_{max,pbo_{TV,ref}} \times \exp\left(E0_{IIV,i} \times E_{max,pboE0}\right)$$

$$E_{max,aba_{TV,i}} = E_{max,aba_{TV,ref}} \times \left(\frac{AGE_i}{AGE_{ref}}\right)^{E_{max,aba\ AGE}}$$

where $P_{TV,ref}$ is the typical value of a parameter (P) at the reference values of all covariates ($E0_{\mathrm{IIV,i}} = 0$, $\mathrm{AGE_{ref}} = 50$ years).

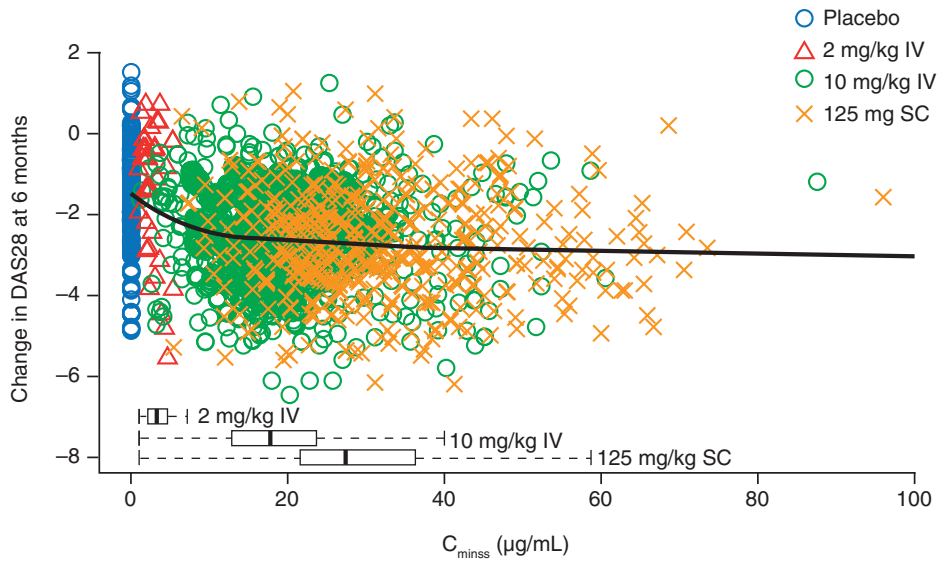

Figure 2. Observed change from baseline DAS28 at month 6 versus C_{minss}. Symbols represent the individual estimates of E_{max}; the curve shows the dependency of the population average estimate of E_{max} on C_{minss}. The box and whisker plots denote the EC50 values and 95%CIs. C_{minss}, steady-state trough concentration; DAS28, 28-Joint Disease Activity Score; IV, weight-tiered intravenous dosing regimen; SC, fixed 125-mg subcutaneous dosing regimen.

The magnitude in improvement for DAS28 (decrease) was higher in patients with higher C_{minss}, such that half-maximal decrease in DAS28 was estimated to be achieved at a C_{minss} value of 6.82 μg/mL (Figure 2). The magnitude of improvement in DAS28 increased rapidly as C_{minss} increased from 5 to 10 μg/mL and continued to increase in smaller increments as concentrations rose above 10 μg/mL, which supports the selection of C_{minss} 10 μg/mL as the target therapeutic exposure. In the time domain, the half-maximal decrease is estimated to occur at about 2 months.

The visual predictive check, which compared observed and model-predicted DAS28 score in patients with RA at actual observation times after first dose, showed that, for all treatment arms, the median, 5th and 95th percentiles of the observed DAS28 scores fell within the 95% CI of the corresponding predicted percentiles, indicating that the final E-R model adequately describes the DAS28–time profile (Figure 3). The DAS28 scores simulated for both the IV and SC treatments are consistent with the observed DAS28 scores from the ACQUIRE study. The simulations show that most of the reduction in DAS28 occurs within the first 2 months and slows down after that.

Efficacy E-R Analysis: American College of Rheumatology 20/50/70 Response Criteria

The E-R ACR20/50/70 analysis dataset included 1893 observations in 1893 patients in the 3 phase 2/3 studies. At baseline, the numbers (%) of patients who were ACR20, 50, and 70 responders were 1304 (68.9%), 819 (43.3%), and 408 (21.6%), respectively.

The base model was an ordered categorical proportional-odds model with C_{minss} as a statistically significant predictor of ACR response. The C_{minss} effect on ACR response is incorporated using a hyperbolic (E_{max}) function on the logit (log-odds). The effect of all of the following prespecified 8 covariates on the log-odds of achieving an ACR response without abatacept were incorporated to the full model: baseline DAS28 score, body weight, age, sex, race, treatment regimen, concomitant corticosteroid use, study. The full model parameter estimates are shown in Table 3.

The covariate effects on the OR of achieving ACR20/50/70 (calculated based on parameters listed in Table 3) are presented in Figure 4. After accounting for exposure (C_{minss}), the effect of SC treatment on ACR20/50/70 response was not significantly different from the effect of IV treatment (OR, 0.877; 95%CI, 0.721–1.10) (Figure 4). Patients with body weight >100 kg had statistically significant decreased odds of achieving an ACR20/50/70 response compared with patients with body weight ≤100 kg (OR, 0.611; 95%CI, 0.442–0.839). However, there was no statistically significant difference in ACR20/50/70 response in patients with body weight <60 kg compared with 60 to 100 kg (OR, 1.06; 95%CI, 0.868–1.300). The study in which patients were enrolled, concomitant corticosteroid use, and race (black vs white or Asian vs white) did not affect ACR20/50/70 response. For the continuous covariates (age and baseline DAS28), the

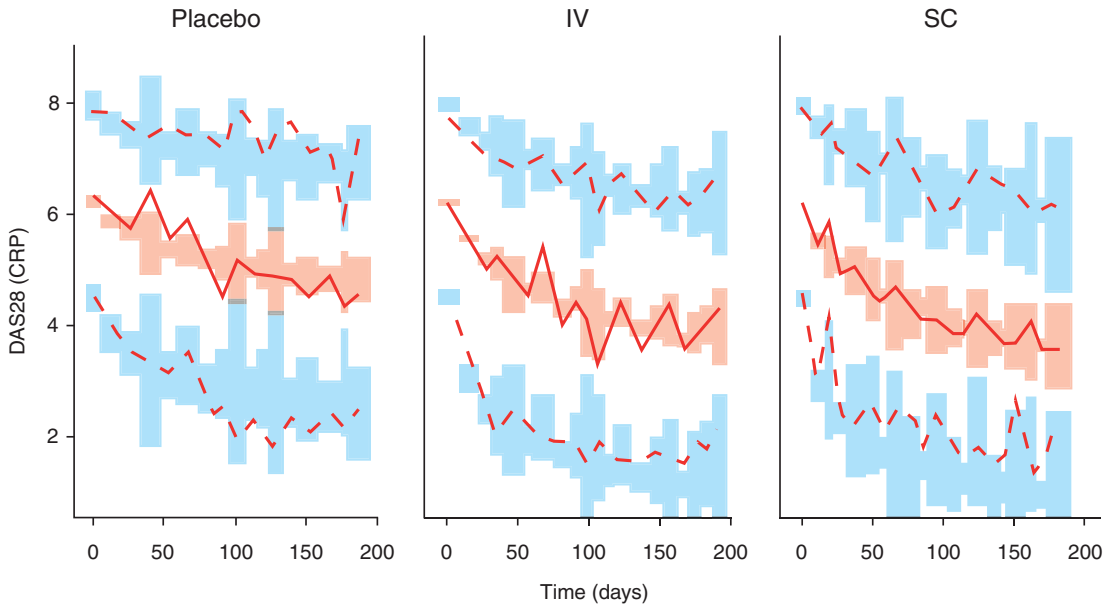

Figure 3. Visual predictive check: observed and simulation-based 95%CIs of DAS28 score up to 6 months (phase 3 ACQUIRE study). The solid red line represents the median observed DAS28, and the semitransparent red field represents a simulation-based 95% confidence interval for the median. The observed 5% and 95% percentiles are presented with dashed red lines, and the 95% confidence intervals for the corresponding model predicted percentiles are shown as semitransparent blue fields. CI, confidence interval; CRP, C-reactive protein; DAS28, 28-Joint Disease Activity Score; IV, weight-tiered intravenous dosing regimen ~10 mg/kg; SC, fixed 125-mg subcutaneous dosing regimen.

OR of ACR response decreased as age increased and as baseline DAS28 decreased.

The final model was evaluated by visual predictive check. The observed proportions of ACR responders were consistent with the 90% prediction intervals, indicating that the model predictions of the probability of ACR response are consistent with the observed data (Figure 5).

The observed ACR20/50/70 response rates across body weight (<60 kg, 60 to 100 kg, >100 kg) and treatment groups (SC and IV) were contained within the model-predicted 95%CI, indicating that the model predictions are consistent with the observed data in each of the subgroups in the phase 3 study (ACQUIRE), in which both IV and SC treatments were tested (Table S5). The model-predicted ACR20/50/70 response rates were lowest for the >100 kg body weight group, and highest for the <60 kg body weight group, for both IV and SC treatment groups. Nonetheless, the model-predicted ACR20/50/70 response rates for IV and SC dosing regimens are similar within each of the weight subgroups.

Discussion

This report is the first comprehensive characterization of abatacept (IV and SC) PK in patients with RA. In addition, it is the first analysis to report the E-R relationship for abatacept clinical efficacy responses (DAS28, a time-continuous measure and ACR response, a binary measure at a specific time) in patients with RA.

The PK of abatacept was time-invariant and was described by a 2-compartment model consistent with the PK behavior exhibited by many other large therapeutic proteins, with first-order absorption with no time delay for SC abatacept. Unlike many monoclonal antibodies, which exhibit nonlinear clearance, abatacept appears to exhibit nearly dose-proportional behavior. This observation corresponds to the dose-proportionality analysis for C_{max} and area under the curve.

Abatacept demonstrated a positive correlation between clearance and body weight as expected based on the mechanism of clearance. Abatacept is a fusion protein (molecular weight [MW]: 92 kDa) that consists of the extracellular domain of cytotoxic T cell–associated antigen 4 linked to the modified Fc (hinge, CH2, and CH3 domains) portion of immunoglobulin G1. Elimination is believed to occur via catabolism by the reticuloendothelial system, and not by renal elimination (given that its MW is higher than that of serum albumin). The macrophages and monocytes that comprise the reticuloendothelial system are distributed throughout all tissues in the body, and therefore it is to be expected that abatacept clearance is greater in patients with higher body weight. The volume of distribution of abatacept is also expected to be greater in patients with higher body weight because of a higher distribution of abatacept into extracellular space. Similarly, many other large molecules have

Table 3. Full E-R ACR20/50/70 Model Parameter Estimates

Name (Units)[a]	Estimate	Standard Error (RSE%)[b]	95% Confidence Interval[c]
β_{ACR20} (–)	–0.182	0.266 (146)	–0.673, 0.352
β_{ACR50} (–)	–1.20	0.0503 (4.19)	–1.31, –1.11
β_{ACR70} (–)	–1.11	0.0502 (4.52)	–1.22, –1.01
EC_{50} (μg/mL)	10.4	4.53 (43.6)	0.0500, 19.7
$E_{max,aba}$ (–)	2.18	0.456 (20.9)	0.846, 2.88
E_0 (–)	0.128	0.0502 (39.2)	0.0285, 0.222
Body weight <60 kg (–)	0.0573	0.102 (178)	–0.141, 0.265
Body weight >100 kg (–)	–0.492	0.163 (33.1)	–0.816, –0.175
Age (–)	–0.0234	0.00356 (15.2)	–0.0307, –0.0165
Sex (–)	–0.220	0.124 (56.4)	–0.469, 0.0237
Treatment (–)	–0.131	0.111 (84.7)	–0.327, 0.0945
Corticosteroid use (–)	0.143	0.107 (74.8)	–0.0534, 0.358
Race: Asian (–)	–0.0814	0.169 (208)	–0.416, 0.238
Race: Black (–)	0.0532	0.284 (534)	–0.515, 0.599
Race: Others (–)	0.393	0.122 (31.0)	0.160, 0.643
Study IM101100 (–)	–0.138	0.204 (148)	–0.590, 0.221
Study IM101102 (–)	–0.287	0.239 (83.3)	–0.821, 0.116

ACR20/50/70, 20, 50, or 70% improvement on American College of Rheumatology response criteria; β_{ACR20}, the log-odds that a patient will achieve an ACR20 response on placebo treatment; β_{ACR50}, the log-odds that a patient will achieve an ACR50 response relative to an ACR20 response; β_{ACR70}, the log-odds that a patient will achieve an ACR70 response relative to an ACR50 response; E_0, Disease Activity Score at baseline; EC_{50}, concentration needed to achieve half of maximum drug response; $E_{max,aba}$, maximum drug response; E-R, exposure-response; RSE, relative standard error.

[a]Reference values for the covariates: baseline DAS28 score = 6, body weight = 60 to 100 kg, age = 50 years, sex = male, treatment = IV, corticosteroid use = no, race = White, study = ACQUIRE.

[b]RSE% is the relative standard error (standard error as a percentage of estimate).

[c]All confidence intervals are from 1703 successful runs from 2000 bootstrap runs.

demonstrated a strong relationship between body weight and PK.[8] The effect of patient body weight is reflected in the recommended body weight–tiered dosing for IV abatacept (~10 mg/kg Q4W; ie, 500 mg/kg for <60 kg, 750 mg/kg for 60 to 100 kg, 1000 mg/kg for >100 kg, Q4W)[2] and confirms previously published results.[5] Following body weight–tiered IV dose administration, C_{minss} was comparable across the body weight subgroups (Figure S1). Age, sex, race, renal function (measured by cGFR), hepatic function (measured by albumin and total bilirubin), and concomitant use of methotrexate, corticosteroid, or NSAIDs had no clinically meaningful effects on abatacept PK, suggesting that no dose adjustment is required for these covariates.

Based on the observations of T_{max} ~4 days with SC abatacept and terminal half-life of ~14 days for both IV and SC abatacept in clinical studies,[2] it is reasonable to constrain $KA > K_{el}$ in the population PK model to prevent flip-flop of parameter estimates and to ensure that the rate of absorption is always higher than the rate of elimination. Following SC administration, the bioavailability of proteins is usually incomplete.[9–11] The SC bioavailability of abatacept in this study was 80.5%, which is consistent with that for other therapeutic proteins of similar size, such as monoclonal antibodies (bioavailability range,[12] 43%–82%). The incomplete bioavailability is due to catabolism by macrophages and monocytes in the tissue prior to entering the system circulation via lymphatic drainage.

The parameters of CL and VC were not highly correlated in the population PK model (correlation coefficient, 0.52; Table 1). The IIV on KA is partitioned into the estimated value of the KA_{IIV} parameter, added to the IIV in $K_{el} = CL/VC$. The KA_{IIV} is not necessarily correlated with the IIV K_{el} as the rate of absorption from a SC depot is not expected to be associated with overall body size.

The E-R analyses for DAS28 indicated that the C_{minss} of abatacept was the best predictor of DAS28 response compared with other measures of exposure (C_{maxss} and C_{avgss}). C_{avgss} was used instead of steady state area under the curve (AUC_{ss}) due to the difference in dosing frequencies for IV and SC regimens (Q4W vs QW). The measure of exposure C_{minss} was selected during base model development by testing the goodness of fit of the model with C_{minss} against alternative models in which C_{minss} was replaced with either C_{maxss} or C_{avgss}. In this way, it was possible to test which of these 3 measures of exposure were the best predictors of efficacy as the data set included both IV and SC data that disrupted the correlation among these measures of exposure. As administration route (IV vs SC) had no significant effect on maximum drug effect, EC_{50}, or T_{50}, it indicates that C_{minss} is a better predictor of efficacy than C_{maxss} and C_{avgss}, irrespective of administration route. Therefore, for a given C_{minss}, the DAS28 response is expected to be the same regardless of route of administration.

The placebo DAS28 response increased with higher baseline DAS28 scores and abatacept DAS28 response decreased as age increased. The placebo response observed in this study is thought to be due to 2 interventions: First, all patients were on a background treatment of methotrexate, and therefore even those on placebo were receiving antirheumatic therapy. Second, patients enrolled in this clinical study were monitored more intensively than patients receiving routine care. The effect of these interventions is more likely to be observed in patients with more severe disease at baseline, where it is easier to see some efficacy than in those with less severe disease. Severity of baseline disease as a significant correlate for the magnitude of response is also widely observed in other therapeutic areas such as type 2 diabetes.[13] Thus, it was not surprising that patients with a higher DAS28 score at baseline had a larger reduction in the placebo effect. Patients who are older have decreased physical functions related to

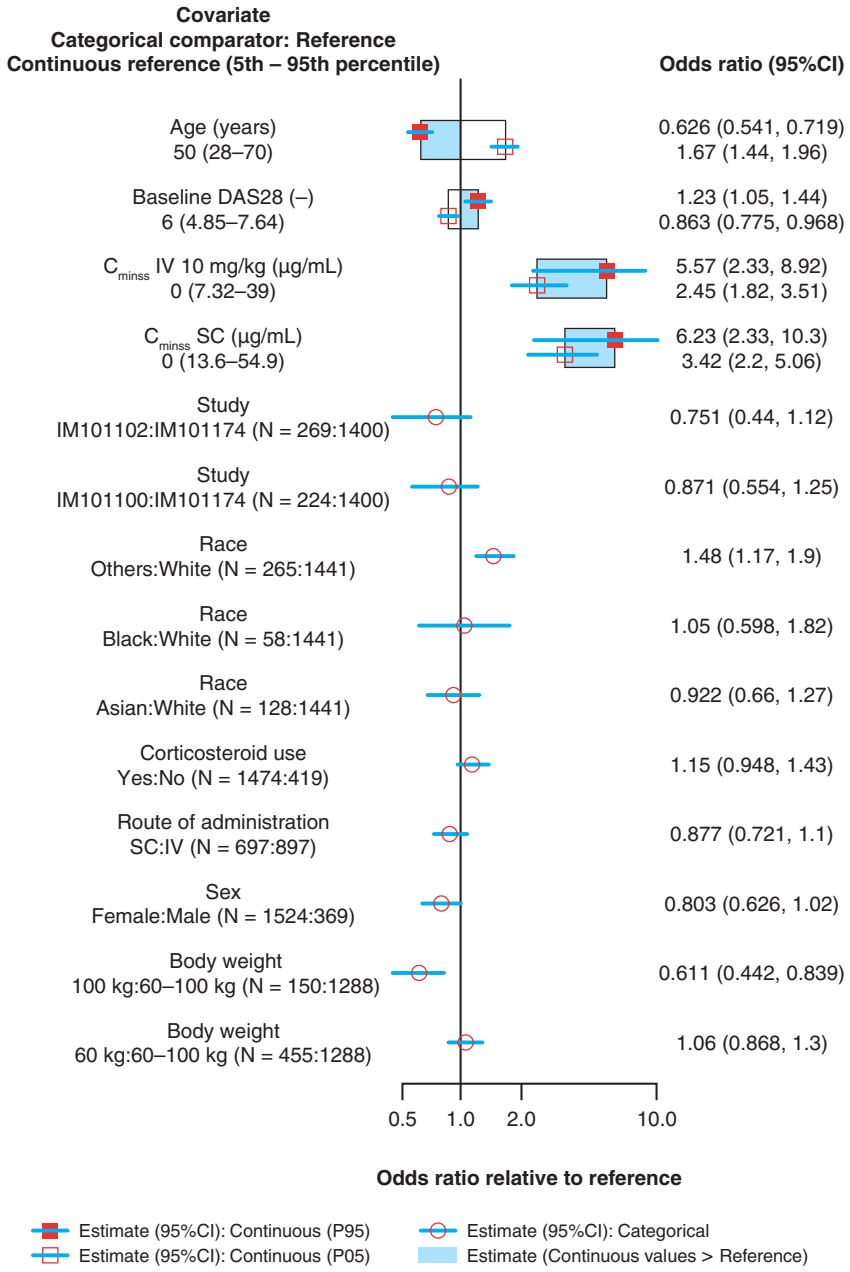

Figure 4. Covariate effects on the odds ratio of achieving ACR20/50/70 for the full model. Reference subject is a 50-year-old white man on IV placebo treatment in ACQUIRE with no corticosteroid use and body weight between 60 and 100 kg, with a baseline DAS28 score of 6. ACR20/50/70, 20%, 50%, or 70% improvement on American College of Rheumatology response criteria; CI, confidence interval; C_{minss}, steady-state trough concentration; DAS28, 28-Joint Disease Activity Score; IV, weight-tiered intravenous dosing regimen ~10 mg/kg; SC, fixed 125-mg subcutaneous dosing regimen.

age and are less likely to respond to abatacept, thus resulting in a decrease of drug response with age.

Indirect response modeling was not used to evaluate ACR20/50/70 since ACR response was evaluated only once (at Month 6) for each patient and no longitudinal data were available to build the model. Compared with using ACR20, ACR50, or ACR70 alone as a single efficacy end point, the ordered categorical proportional-odds model (the most widely used logistic regression model for ordered categorical responses[14]) of ACR20/50/70 response also takes into account whether a patient achieves the different levels of ACR response (ACR20, ACR50, or ACR70) simultaneously. Inclusion of ACR20/50/70 in this analysis is also particularly relevant, as all 3 of these ordered categorical efficacy end points are derived from the same underlying continuous valued efficacy variable, namely, the percentage improvement in ACR score (commonly abbreviated as ACRN).[15] Consistent with the results shown in the DAS28 E-R analysis, the odds

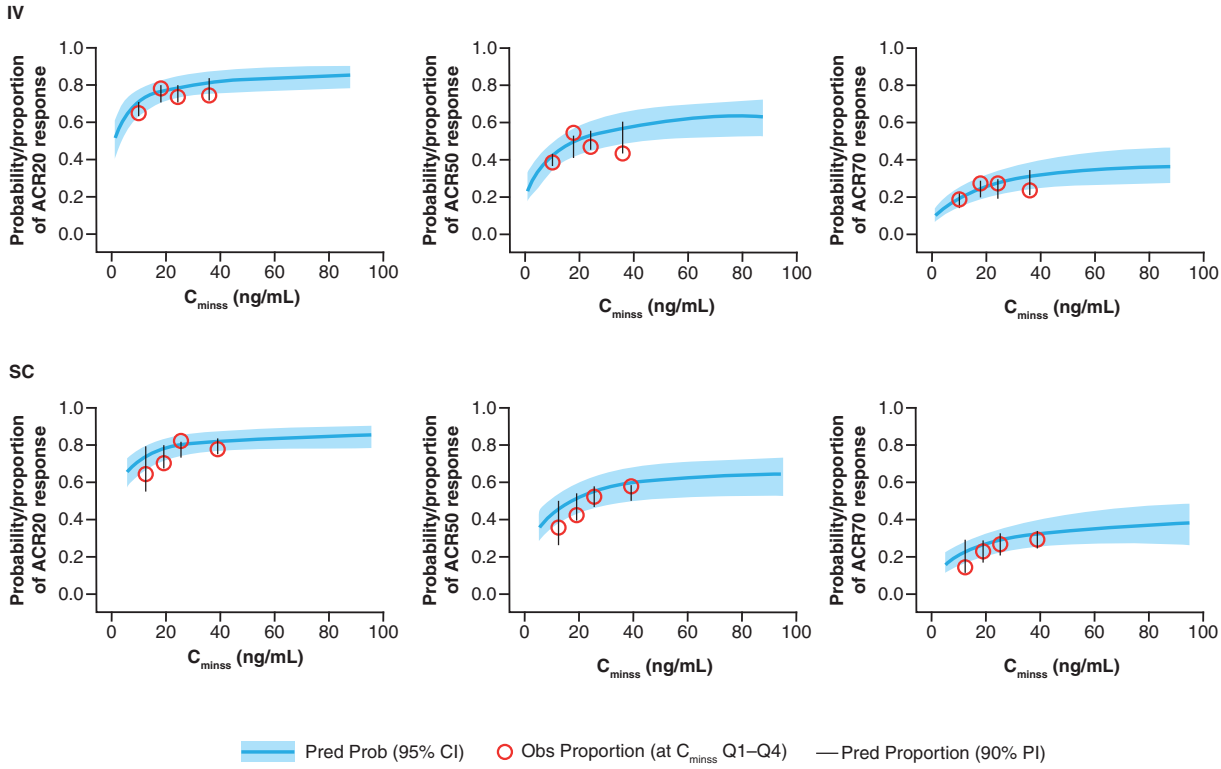

Figure 5. Visual predictive check: predicted probability/proportion of ACR responses vs C_{minss} (phase 3 ACQUIRE study). The observed and predicted proportions of each quartile are plotted at the median of the C_{minss} quartile. The 90% PI represents the PI of the proportion of responders in each C_{minss} quartile, conditional on the point estimate (uncertainty is not considered). The 90%PI was generated from the 5th and 95th percentiles of the proportion of responders, which was obtained by simulation with the model-predicted probability. The blue shaded band is the 95%CI for the predicted probability at the reference values of covariates, representing the uncertainty in the predicted probability with regard to concentration. The 95%CI was determined by randomly sampling the values of the intercepts, EC_{50}, and E_{max}, from the multinormal distribution given by the point estimate of these parameters and the variance covariance uncertainty matrix of these estimates. ACR20/50/70, 20%, 50%, or 70% improvement on American College of Rheumatology response criteria; CI, confidence interval; C_{minss}, steady-state trough concentration; EC_{50}, concentration needed to achieve half of maximum drug response; E_{max}, maximum ACR response; IV, weight-tiered intravenous dosing regimen ~10 mg/kg; Obs, observed; PI, prediction interval; Pred, predicted; Prob, probability; Q, quartile; SC, fixed 125-mg subcutaneous dosing regimen.

of abatacept ACR response decreased as age increased and as baseline DAS28 decreased. Consistent results were seen for both the E-R DAS28 and ACR20/50/70 analyses in which, for both IV and SC treatment, the efficacy responses increased with increasing abatacept C_{minss}, and approached a plateau at C_{minss} >10 μg/mL.

Treatment with IV abatacept is approved as a weight-tiered dose regimen (500, 750, and 1000 mg for patients weighing <60 kg, 60 to 100 kg, and >100 kg, respectively).[2] The fixed SC abatacept dose of 125 mg was demonstrated to be therapeutically equivalent to the weight-tiered IV dosing in RA. For the weight-tiered IV abatacept, the efficacy responses plateaued at C_{minss} >10 μg/mL across the body weight groups, which represents the maximum dose to observe improvements in efficacy. For SC abatacept, all body weight groups received the fixed dose of 125 mg QW. Lower levels of abatacept were anticipated in the higher body weight groups (>100 kg); however, the median trough concentration in the highest body weight group (>100 kg) with the SC dosing regimen was similar to that achieved with the IV dosing regimen. From the simulation, for both IV and SC treatments, ~90% of patients achieved a trough concentration of 10 μg/mL, which was associated with the near-maximal efficacy response; thus, even though the C_{minss} of SC treatment in the overall population is higher than the C_{minss} of IV treatment, the response rate did not differ in the 2 treatment groups. Model-predicted response rates for the IV and SC abatacept treatments were similar, which supports the label-recommended flat SC dosing for SC abatacept (125 mg QW). Data from the phase 3 ACQUIRE study confirmed the therapeutic equivalence between the weight-tiered IV dosing regimen and a flat SC dosing regimen.[3] The fixed SC abatacept dose was proposed (and later approved) by bridging to the approved weight-tiered IV abatacept. Subgroup analysis showed that despite numerically lower ACR20 response rates in the >100 kg vs the <60 or 60 to 100 kg subgroups, there were no clinically relevant differences

in efficacy, safety, and immunogenicity between the profiles of SC and IV abatacept by body weight subgroup.

Conclusions

The population PK model adequately and simultaneously described IV and SC abatacept PK in patients with RA. Body weight was a significant covariate impacting the PK of abatacept and, consequently, the abatacept labeled IV dosing regimen is weight tiered. The efficacy E-R DAS28 analysis showed that C_{minss} was the best and a sufficient exposure predictor for efficacy responses, with a $C_{minss} > 10$ μg/mL associated with the near-maximal efficacy response (plateau). The E-R relationships between C_{minss} and efficacy responses (DAS28 and ACR20/50/70) were the same for both IV and SC abatacept. By achieving $C_{minss} > 10$ μg/mL across body weight groups, the fixed SC abatacept treatment demonstrated clinical equivalence to the weight-tiered IV treatment, achieving the near-maximal efficacy response for both IV and SC dosing regimens.

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Declaration of Conflicting Interests

X.L. was an employee of, and held stock options and/or bond holdings in, Bristol-Myers Squibb at the time that the work was performed. A.R. and B.M. are employees of, and hold stock options and/or bond holdings in, Bristol-Myers Squibb.

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Author Contributions

All authors contributed to the writing of the manuscript, designed and carried out the study research, analyzed the data, and agree to be accountable for all aspects of the work.

Data Sharing Statement

Bristol-Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.