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Model-Based Selection and Recommendation for Subcutaneous Abatacept Dose in Patients With Polyarticular Juvenile Idiopathic Arthritis

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Abstract

The selective T-cell costimulation modulator abatacept is approved for treatment of adult rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (pJIA; 6-17 years [intravenous] and 2-17 years [subcutaneous]). An extrapolation approach was taken to determine subcutaneous weight-tiered doses of abatacept to evaluate in patients with pJIA. Population pharmacokinetic (PPK) and exposure-response (E-R) analyses were conducted to determine whether the weight-tiered subcutaneous regimen provides near-maximal efficacy and is therapeutically comparable to the intravenous regimen in patients with pJIA aged 2-17 years. Combined study data from intravenous or subcutaneous abatacept were used to assess clinically relevant exposure outcomes. The PPK model was developed with data from 13 phase 2/3 studies in RA and pJIA; the E-R model for the American College of Rheumatology pediatric scores (JIA-ACR 30/50/70/100 responses) in month 4 was developed with data from 2 phase 3 pJIA studies. Predefined covariates were investigated in both analyses. PPK model-predicted exposures were steady-state peak, trough (C_{minss}), and time-averaged concentrations. Abatacept PK was characterized by a linear 2-compartment model (zero-order intravenous infusion, first-order subcutaneous absorption, first-order elimination); body weight was the only clinically relevant covariate. C_{minss} was the best exposure predictor for the JIA-ACR response: log odds for response increased in proportion to log-transformed C_{minss}; JIA-ACR30 approached a plateau when $C_{minss} \geq 10$ μg/mL. The PPK and E-R analyses demonstrated that the weight-tiered subcutaneous and intravenous abatacept dosing regimens provide near-maximal efficacy and are clinically comparable across children with pJIA who are $>$ 2 years old.

Keywords

abatacept, population pharmacokinetics, juvenile idiopathic arthritis, JIA-ACR, exposure-response, pediatric

Polyarticular juvenile idiopathic arthritis (pJIA) is the most common chronic rheumatic disorder in children and a leading cause of childhood-acquired disability.[1] Treatment of pJIA with biologic disease-modifying antirheumatic drugs (bDMARDs) is now well established and has led to improved clinical outcomes.[2] Abatacept, a selective T-cell costimulation modulator, has a mechanism of action that is fundamentally different from that of other bDMARDs (such as tumor necrosis factor inhibitors and interleukin-6 receptor inhibitors).[3]

Intravenous and subcutaneous abatacept have been shown to be effective and well tolerated in clinical trials and real-world studies in patients with rheumatoid arthritis (RA)[4–10] and pJIA,[11–14] with benefits sustained for up to 7 years in patients with pJIA aged 6 to 17 years.[12,14]

The recommended therapeutic intravenous and subcutaneous abatacept doses were informed by population PK and exposure-response (E-R) analyses of data from weight-tiered intravenous (~10 mg/kg every 4 weeks [Q4W]) and fixed-dose subcutaneous (125 mg weekly) abatacept in adult patients with RA[15] and weight-normalized (10 mg/kg Q4W) intravenous abatacept in patients with pJIA. These analyses showed that clinical efficacy was near maximal at an abatacept steady-state trough concentration (C_{minss}) of 10 μg/mL. In addition, in patients with RA, weight-tiered intravenous and fixed-dose subcutaneous abatacept dosing was shown to be clinically equivalent in a randomized

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phase 3 study as well as by population PK and E-R analyses.[4,15]

Here we report on the population PK and E-R analyses that were performed to select weight-tiered subcutaneous doses for patients with pJIA, as well as analyses of the data from the clinical study confirming that the selected doses achieved the target exposures (the primary end point of the study). These data and analyses are the basis for the recommended weight-tiered subcutaneous abatacept dosing regimen in patients with pJIA.[16,17]

Methods

Data and Study Populations

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

Data from 13 phase 2/3 studies of intravenous and subcutaneous abatacept were analyzed to assess clinically relevant exposure outcome measures (Table S1). Eleven studies included adult patients with RA, and 2 studies included patients with pJIA aged 2-17 years. A total of 12 759 samples (RA, 9420; pJIA, 3339) from 2616 patients (RA, 2213; pJIA, 403) were included in the population PK analysis. Dosing and routes of administration for each study are shown in Table S1.

Dose Selection of Subcutaneous Abatacept for pJIA

A similar range of C_{minss} concentration (≥ 10 μg/mL) as intravenous abatacept in patients with pJIA was targeted for selecting subcutaneous doses of abatacept for clinical evaluation in patients with pJIA while remaining within the range of observed exposures as subcutaneous abatacept in RA. This was done for the following reasons: (1) the efficacy of intravenous abatacept in patients with pJIA was adequately described by C_{minss},[18] and (2) the results of the E-R analysis of subcutaneous and intravenous abatacept in patients with RA showed that C_{minss} was the best and a sufficient predictor of efficacy response.[15]

Determination of subcutaneous abatacept doses that produce $C_{minss} \geq 10$ μg/mL in patients with pJIA across all body weights was accomplished by simulation with a population PK model. To this end, the existing population PK model[18] for intravenous abatacept in patients with pJIA was adapted to predict exposures following subcutaneous abatacept by leveraging 2 existing abatacept population PK models: (1) a model describing intravenous abatacept PK in patients with pJIA and patients with RA (Model 1) and (2) a model describing intravenous and subcutaneous abatacept PK in patients with RA (Model 2). These models were combined to formulate a preliminary population PK model for intravenous and subcutaneous abatacept in patients with pJIA (Model 3), which was then used to predict subcutaneous abatacept exposures.

Model 3 assumes that the parameters describing the rate and extent of subcutaneous absorption in patients with pJIA are the same as in adult patients with RA. This was considered a reasonable assumption because the transport processes governing subcutaneous absorption were expected to be similar in adults and pediatric patients: similar values for the absorption rate constant of another fusion protein (etanercept) have been reported for patients with pJIA and adult patients with RA,[19,20] and age and body size were not significant covariates for model parameters describing the absorption kinetics for abatacept (Model 2).

Population PK Analysis of Subcutaneous Abatacept for pJIA

The population PK analysis data set included all patients from the studies listed in Table S1 for whom abatacept serum concentration data were available. Abatacept serum concentrations were measured by a validated enzyme-linked immunosorbent assay, with a lower limit of quantification of 1.0 ng/mL. End of infusion and trough serum samples were collected from pediatric and adult patients, and additional serum samples were collected in adults to determine the plasma concentration-time profile of abatacept. Abatacept serum concentrations below the lower limit of quantification were excluded from the analysis (8.7% of samples were excluded). Missing serum concentrations and sample collection times were not replaced with imputed values. Missing dosing information (dose amount, infusion duration, dosing time, and dosing date) were imputed to maximize the inclusion of abatacept concentration following subsequent doses. Graphical outliers were identified as concentrations that were substantially different and higher relative to other concentrations in patients receiving the same dosing regimens and were excluded from the analysis.

The population PK model of abatacept was developed in 3 stages (base, full, and final models) as described previously[15] and shown in Figure S1. The previously developed base structural model[15] was reestimated using the pooled intravenous and subcutaneous JIA and RA data.

The base model development consisted of determining 3 component models: a structural PK model, an interindividual model, and a residual variability model. Bioavailability included in the population PK model was the absolute bioavailability for subcutaneous

Table 1. Predefined Covariates Investigated in the Population PK and Exposure-Response Analyses

Baseline Covariates	Population PK Analysis	E-R Analysis
Continuous		
Age, years	Y	Y
Body weight, kg	Y	Y
Albumin, g/dL	Y	
Calculated GFR, mL/min/1.73 m^2	Y	
Total bilirubin, mg/dL	Y	
TJC	Y	Y
SJC	Y	Y
C-reactive protein, mg/dL		Y
Physician Global Assessment of Disease Activity		Y
Categorical		
Sex (male vs female)	Y	Y
Race (white vs nonwhite)	Y	Y
Disease (pJIA vs RA)	Y	
Baseline disease duration ($\leq$ 2, 2-5, $>$ 5 to 10, and $>$ 10 years)	Y	Y
Methotrexate use at baseline (yes vs no)	Y	Y
Corticosteroid use at baseline (yes vs no)	Y	Y
NSAID use at baseline (yes vs no)	Y	Y
Administration route (subcutaneous vs intravenous)		Y
Prior anti-TNF-α use (yes vs no)		Y
pJIA category (persistent oligoarthritis, systemic arthritis, and all other subtypes vs combined polyarticular RF+ and polyarticular RF−)		Y
Immunogenicity (positive vs negative)		Y

GFR, glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; pJIA, polyarticular juvenile idiopathic arthritis; PK, pharmacokinetic; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; TNF-α, tumor necrosis factor-α; Y, yes.

administration of abatacept. As absolute bioavailability is bound between 0 and 1, the absolute bioavailability was modeled using the inverse logit function (Supplementary Equation S1).

To ensure that the rate of absorption was always higher than the rate of elimination (and thereby avoid flip-flop kinetics), individual absorption rate constant (KA) was expressed as the sum of the individual estimated relative rates of absorption and the individual rate of elimination (Supplementary Equation S2).

A full model was then developed by incorporating the effects of all prespecified covariates on structural model PK parameters (Table 1). The relationship between PK parameters and a continuous-valued covariate (Supplementary Equation S3), and the relationship between the population average of a parameter and a categorical covariate were tested (Supplementary Equation S4). For continuous variables, the reference values were the median values in the population PK data set, and for categorical covariates, the reference values were the mode in the population PK data set, except for sex, for which male was used as the reference.

Exploratory graphical assessment of immunogenicity, selected hepatic function tests (alanine transaminase and aspartate aminotransferase), and baseline anti–tumor necrosis factor inhibitor use (yes vs no) were performed for the pJIA studies because the corresponding information for the RA studies was not available and precluded inclusion in the formal covariate testing.

The final model was developed by backward elimination of covariates from the full model, using a significance level of .001 (which corresponds to an increase in the objective function of 10.83 or 13.82, for 1 or 2 degrees of freedom, respectively). All remaining covariates were significant ($P < .001$). The relationship of clearance (CL) to the covariates in the final population PK model was calculated using Supplementary Equation S5.

A continuous covariate was considered potentially clinically relevant if its inclusion resulted in the 95% confidence interval (CI) for the 5th and 95th percentiles of the covariate exceeding the range of 80% to 125% of the typical value of the PK parameter (including all other covariates in the model).[15] For a categorical covariate, potential clinical relevance was defined as the 95%CI exceeding the range of 80% to 125% of the typical value with this covariate. For both continuous and categorical covariates, covariates that resulted in less than −20% or +25% change in point estimates, and 95%CIs that fell within 80% to 125% of the reference values were determined to be not clinically relevant. The prespecified relevant covariates investigated are shown in Table 1. The final population PK model was used to generate predictions of abatacept steady-state peak concentration (C_{maxss}), C_{minss}, and abatacept steady-state time-averaged concentration (C_{avss}) in patients with pJIA.

The final population PK model evaluation was performed using prediction-corrected visual predictive check (pcVPC) of the model-predicted concentrations versus time after previous dose by patient type (RA and pJIA) and by route of administration (intravenous and subcutaneous).

Exposure-Response Analysis of Subcutaneous Abatacept for pJIA

The E-R model for ACR Pediatric 30, 50, 70, or 100 response criteria (JIA-ACR30/50/70/100) describes the probability of achieving cumulative JIA-ACR responses at 4 months as a function of abatacept exposure using a proportional odds model, in which the log odds (logit) of JIA-ACR was given by a series of expressions, each describing the probability that the response achieved was at least as good as the level specified (ie, $P\ [Y \geq 30\%] = P$ [JIA-ACR30]; Supplementary Equation S6).

The modeling was conducted in 4 stages. First, summary measures of abatacept exposure were determined in patients with pJIA aged 2-17 years (n = 403) derived from the population PK analyses of the 2 phase 3 studies and were used as predictors of clinical response.[12,14] Second, abatacept exposure measures (C_{maxss}, C_{minss}, and C_{avss}) were evaluated to determine the existence of and best functional form for the relationship between abatacept exposure and JIA-ACR response in the base model. Third, a full model was developed incorporating the effects of statistically significant prespecified covariate-parameter relationships (Table 1). The relationship between E-R parameters and a continuous-valued covariate and a categorical covariate was tested as described in the population PK analysis above. For categorical covariates, the number of patients in each category had to exceed 10% of the total number of patients. For race, all nonwhite patients were combined into a single category. A single round of forward selection was used to select covariates determined to be statistically significant when evaluated univariately using an α level of .01 for inclusion. Last, the final model was developed by backward elimination of the covariate effects (α level of .001) included in the full model. The adequacy of fit of the E-R model was evaluated using a VPC.

Application of the Population PK and E-R Models

Stochastic simulations were performed using the final population PK and E-R models to simulate expected distributions of abatacept exposure measures and the probability of JIA-ACR response in month 4. Abatacept exposure in month 4 by route of administration was compared by age group for patients with pJIA (ranges of 2 to < 6, 6 to < 12, and 12-17 years).

All exploratory analyses and presentations of data were performed using SAS version 9.2, R version 2.10.1 (R Foundation for Statistical Computing, Vienna, Austria), and KIWI version 1.5 (Cognigen Corporation, Buffalo, New York). The population PK and efficacy E-R analyses were performed using the NONMEM computer program (version VII, level 3.0; Icon Development Solutions, Hanover, Maryland).

Results

Dose Selection of Subcutaneous Abatacept in Patients With pJIA

Figure S2 illustrates the predicted distribution of C_{minss} across a range of weight-normalized subcutaneous abatacept doses for the overall population. Weight-normalized dosing may be prone to errors, including dosing errors, inadvertent contamination, and the temptation to administer unused solution in place of discarding it. To simplify administration for caregivers and minimize errors, a weight-tiered dosing approach for subcutaneous abatacept was selected to provide $C_{minss} \geq 10$ μg/mL.

Abatacept C_{minss} exposure in patients with pJIA weighing 10-100 kg was simulated by applying the derived subcutaneous population PK model (Model 3). The following subcutaneous abatacept doses were selected, such that > 95% of patients with pJIA would achieve a $C_{minss} \geq 10$ μg/mL: < 25 kg, 50 mg; 25 to < 50 kg, 87.5 mg; ≥50 kg, 125 mg (Figure S3).

The selected weight-tiered subcutaneous abatacept weekly dosing regimen was predicted to produce higher C_{minss} compared with the intravenous dosing recommendation of 10 mg/kg Q4W (Figure S4). However, C_{maxss} and C_{avss} were predicted to be lower in the weight-tiered subcutaneous abatacept dosing regimen versus the 10 mg/kg Q4W intravenous dosing regimen, which has been previously shown to be safe and efficacious.[12] Similar differences between intravenous and subcutaneous administration for measures of systemic exposure were observed in adult patients with RA.[15]

As a result of the model-based PK predictions, the phase 3 pJIA subcutaneous trial in children aged 2-17 years old was designed in an open-label manner using C_{minss} as a primary end point in patients aged 6-17 years old (as a surrogate for efficacy) along with JIA-ACR measures.[14] The weight-tiered subcutaneous abatacept dosing regimen of 50, 87.5, and 125 mg administered weekly to patients with pJIA weighing < 25, 25 to < 50, and ≥ 50 kg, respectively, was evaluated in this phase 3 trial.[14] The objective of this dosing regimen was to deliver abatacept C_{minss} concentrations of at least 10 μg/mL in > 90% of patients across all body weights throughout the age range of 2 to 17 years of age.

Pharmacokinetics of Subcutaneous Abatacept in Patients With pJIA

The selected weekly weight-tiered subcutaneous abatacept dosing regimen achieved the desired target therapeutic C_{minss} (≥10 μg/mL) in 130 of 131 patients with evaluable PK data. As shown in Figure S5, the observed C_{minss} values in the 2- to < 6- and 6- to 17-year-old cohorts are plotted along with Model 3-simulated abatacept concentrations (see Dose Selection of Subcutaneous Abatacept in Patients With pJIA section). These simulated concentrations were derived using Model 3, which included data from subcutaneous and intravenous abatacept in patients with RA and intravenous abatacept in patients with pJIA and was developed prior to conducting the phase 3 study in patients with pJIA treated with subcutaneous abatacept. The observed C_{minss} from patients with pJIA administered subcutaneous abatacept was generally higher than the simulated data, suggesting that assumptions about absorption parameters in pediatric patients being similar

Table 2. Parameter Estimates of the Final Population PK Model Fitted to Expanded Data Set of RA and pJIA Studies Including Data From the 2 to < 6-Year-Old Cohort

	Final Parameter Estimate		Interindividual Variability/Residual Variability		
Parameter (Units)	Typical Value	%RSE	Estimate	%RSE	ETA Shrinkage
KA (L/h)	0.00521	11.0	1.11	24.4	74.9%
VC (L)[a]	3.29	1.57			
Power of body weight on VC	0.603	6.99	0.0464	14.6	61.5%
Power of age on VC	0.114	23.4			
CL (L/h)[a]	0.0179	1.36			
Power of body weight on CL[b]	0.706	2.93			
Power of GFR on CL[b]	0.259	7.19			
Power of albumin on CL[b]	−0.722	9.69	0.0637	4.25	14.3%
Power of SJC on CL[b]	0.0742	12.8			
Exponent of NSAID on CL[b]	0.102	12.5			
Exponent of male sex on CL[b]	0.0674	21.4			
VP (L)[a]	3.67	3.71	0.154	15.9	54.7%
Power of body weight on VP	0.575	7.20			
Intercompartmental CL (L/h)	0.0231	7.25	NE	NA	NA
Bioavailability of SC formulation[a]	0.770	6.09			
Exponent of JIA on bioavailability	3.08	41.3	0.516	15.0	49.2%
Power of body weight on bioavailability	−0.506	27.3			
Power of age on bioavailability	0.487	27.1			
Proportional residual error	NA	NA	0.0615	3.29	12.3%
Additive residual error	NA	NA	0.00134	69.3	12.3%
Minimum value of the objective function = 65 061.705					

CL, clearance; GFR, glomerular filtration rate; KA, absorption rate constant; NA, not applicable; NE, not estimated; NSAID, nonsteroidal anti-inflammatory drug; pJIA, polyarticular juvenile idiopathic arthritis; PK, pharmacokinetic; RA, rheumatoid arthritis; RSE, relative standard error; SJC, swollen joint count; VC, volume of the central compartment; VP, volume of the peripheral compartment.

[a] CL, VC, VP, and bioavailability are typical values of these variables at the reference covariate values. Covariate effects were estimated relative to a reference 49-year-old patient with RA who is female weighing 68 kg with a GFR of 99.18 mL/min/1.73 m^2, baseline albumin level of 4.1 g/dL, and swollen joint count of 15 and not on NSAIDs.

[b] $CL_{TV} = CL_{TV,ref}\left(\frac{BWT_b}{BWT_{ref}}\right)^{CL_{BWT}} \times \left(\frac{cGFR_b}{cGFR_{ref}}\right)^{CL_{cGFR}} \times \left(\frac{ALB_b}{ALB_{ref}}\right)^{CL_{ALB}} \times \left(\frac{BSJC_b+1}{BSJC_{ref}+1}\right)^{CL_{SWOL}} \times \exp(SEX \times CL_{SEX} + NSAID \times CL_{NSAID})$.

to adults may not be valid. The median abatacept C_{minss} value on day 113 in patients with pJIA was 41.6 μg/mL (range, 9.3-122.1 μg/mL; n = 131) in patients aged 2 to 17 years old, 51.2 μg/mL (range, 20.1-122.1 μg/mL) in patients aged 2 to < 6 years old and 40.5 μg/mL (range, 9.3-97.0 μg/mL) in patients aged 6-17 years.

Population PK Analysis of Subcutaneous Abatacept for Patients With pJIA

The intravenous and subcutaneous abatacept population PK model in patients with RA and pJIA was refined using data from a phase 3 study of subcutaneous abatacept in pJIA (Table 2).[21] Figure 1 shows that the magnitude of all categorical covariate effects were generally encompassed within 80%-125% of the reference values. Body weight was considered the only covariate to have a potentially relevant impact on CL, volume of the central compartment (VC), and volume of the peripheral compartment (VP), for which the effect exceeded the 80%-125% range (37%, 30%, and 30% increase in CL, VC, and VP, respectively) at the 95th percentile of body weight (108 kg). Disease (pJIA vs RA) did not have a clinically relevant effect on abatacept CL. In addition, age, sex, and concomitant medications at baseline (including methotrexate, corticosteroids, and nonsteroidal anti-inflammatory drugs) did not influence abatacept CL.

The pcVPC plots showed that the model adequately characterized the data from the 5th to the 95th percentiles. Most of the lines representing the 5th, 50th, and 95th percentiles of the observed data were within the respective 95% prediction interval of the PK data (Figure 2). In patients with pJIA, abatacept C_{minss} values were ~3-fold higher after subcutaneous abatacept administration than after intravenous administration (Figure 3). Subcutaneous weight-tiered abatacept doses achieved a C_{minss} that exceeded the target exposure for near-maximal efficacy ($C_{minss} \geq 10$ μg/mL).

Abatacept exposure measurements at steady state in patients with pJIA were slightly higher in younger

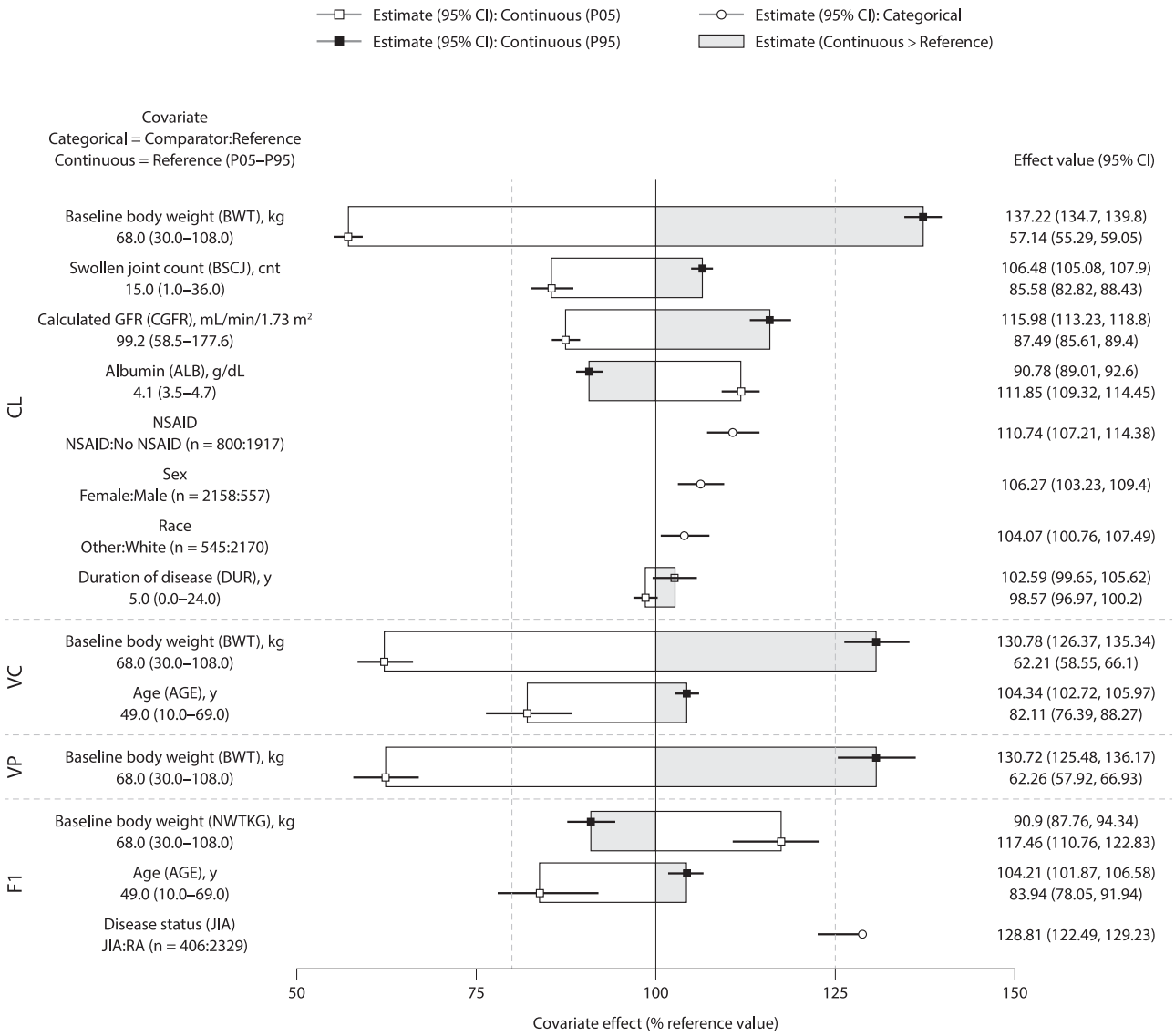

Figure 1. Covariate effect forest plot based on full population PK model. Covariate effects were estimated relative to a reference 49-year-old patient with RA who is female weighing 68 kg with a GFR of 99.18 mL/min/1.73 m^2, baseline albumin level of 4.1 g/dL, and swollen joint count of 15 and not on NSAIDs. CL, clearance; F1, bioavailability; GFR, glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; PK, pharmacokinetics; VC, volume of the central compartment; VP, volume of the peripheral compartment.

and lighter patients; however, the range of abatacept exposures overall was similar between different weight-tiered dose regimens and age groups following subcutaneous administration (Figure 3), suggesting that weight-tiered subcutaneous dose regimens were able to provide exposures similar to those in patients with pJIA across different age groups and weight categories. Across different administration routes in patients with pJIA, C_{minss} values (target, ~10 ug/mL) were ~3-fold higher after subcutaneous administration, whereas C_{avss} values were similar following intravenous and subcutaneous administration (Figure S6). As expected, the C_{maxss} value was considerably higher following intravenous versus subcutaneous administration. Overall, within the same administration route (10 mg/kg intravenous or weight-tiered subcutaneous doses), exposures were similar between age groups in patients with pJIA.

From exploratory graphical assessments, there appeared to be no obvious difference in CL when stratified by antidrug antibody (ADA) status suggesting that ADA had no impact on the PK of abatacept for patients with pJIA aged 2 to 17 years (Figure S7). Similar results were observed when assessing the impact of prior anti-TNF use on abatacept CL.

There appeared to be a negative trend between CL and aspartate transaminase (AST) when AST was < 40 U/L (within normal AST reference range) and a

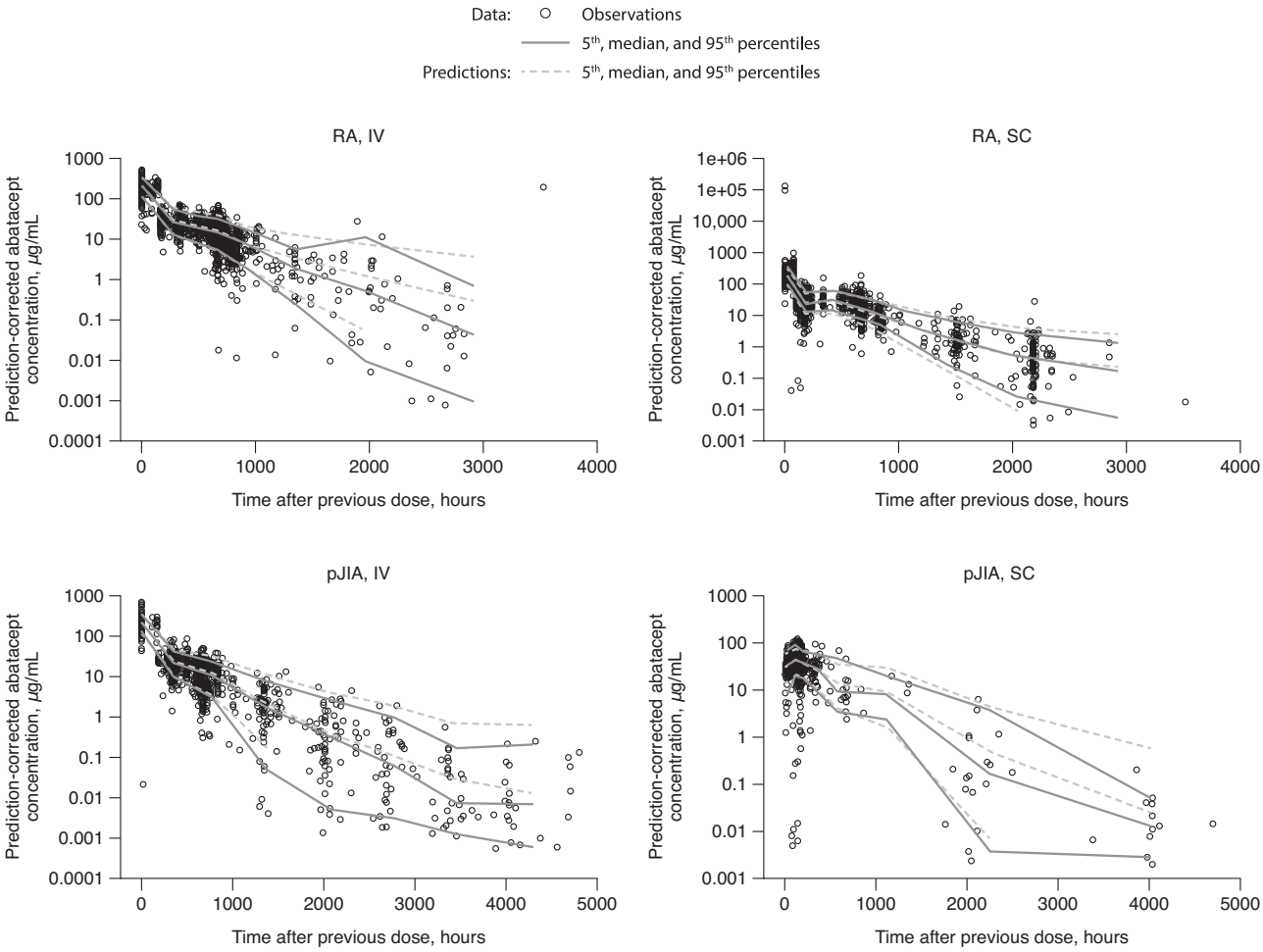

Figure 2. pcVPC of the final population PK model for RA (intravenous and subcutaneous abatacept) and pJIA (intravenous and subcutaneous abatacept). Median and percentiles are plotted at the midpoint of each time after the previous dose interval. CI, confidence interval; IV, intravenous; pcVPC, prediction-corrected visual predictive check; pJIA, polyarticular juvenile idiopathic arthritis; PK, pharmacokinetic; RA, rheumatoid arthritis; SC, subcutaneous.

slight positive trend between CL and alanine aminotransaminase (ALT) < 40 U/L (within normal ALT reference range). These results suggest that there might be little impact of hepatic function on the PK of abatacept. Given the small amount of data at high values of AST or ALT (ie, 40-200 U/L), no conclusion can be drawn regarding the relationship between abatacept CL and baseline AST or ALT at values beyond the normal reference ranges.

Abatacept C_{maxss}, C_{minss}, and C_{avss} by route and dose for patients with pJIA and patients with RA were examined and are displayed in Figures S8, S9, and S10, respectively. Overall, the steady-state exposure measurements were similar between patients with pJIA and patients with RA following the same administration route. For patients receiving subcutaneous doses, patients with pJIA tended to have slightly higher exposure compared with patients with RA, but the ranges were generally within the range seen in RA with subcutaneous abatacept. For patients following intravenous doses, the steady-state exposure was generally comparable between patients with JIA and patients with RA.

Exposure-Response Analysis of Subcutaneous Abatacept for pJIA

A total of 403 patients aged 2-17 years (98.5%) were included in the E-R analysis. There was a significant relationship between exposure and JIA-ACR response, with abatacept C_{minss} being the best predictor of response (Table S2). Abatacept C_{maxss} and C_{avss} were highly correlated with C_{minss} ($r \geq 0.66$ or $r \leq -0.66$). A C_{minss} of 10 μg/mL was associated with the near-maximal JIA-ACR30 response in patients with pJIA. The probability of achieving an JIA-ACR response in month 4 was found to increase with increasing C_{minss}. JIA-ACR response was best described by a log-linear function of C_{minss} for both intravenous

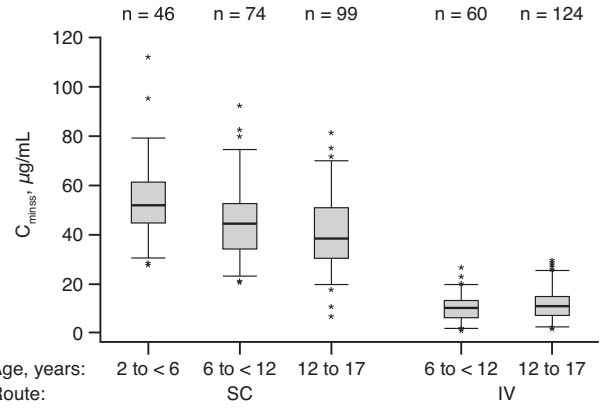

Figure 3. Predicted distributions of abatacept C_{minss} following intravenous and subcutaneous administration in patients with pJIA by age category. Boxes are 25th, 50th, and 75th percentiles; whiskers are 5th to 95th percentiles. Asterisks show data points outside this range. The number of patients is below each box. C_{minss}, steady-state trough concentration; IV, intravenous; pJIA, polyarticular juvenile idiopathic arthritis; SC, subcutaneous.

Table 3. Parameter Estimates of the Final Exposure-Response Model for Probability of JIA-ACR Response

Parameter	Estimate (RSE%)
Intercept for JIA-ACR30 (logit)	1.47 (8.94)
Intercept for JIA-ACR50 (logit)	−0.618 (13.9)
Intercept for JIA-ACR70 (logit)	−0.826 (11.0)
Intercept for JIA-ACR100 (logit)	−1.86 (8.01)
Slope for log(C_{minss}), 1/(μg/mL)	0.803 (12.8)
Minimum value of the objective function = 1172.207	

ACR30/50/70/100, American College of Rheumatology measuring 30%/50%/70%/100% improvement on a scale of 28 intervals; C_{minss}, steady-state trough concentration; JIA, juvenile idiopathic arthritis; RSE, relative standard error.

and subcutaneous administration. Final parameter estimates are presented in Table 3.

Univariate forward selection was performed to evaluate covariate effects on the probability of JIA-ACR response after accounting for abatacept exposure. The effects of C-reactive protein, age, and swollen joint count at baseline were found to be statistically significant (Figure S11). No covariates were significant predictors of the probability of JIA-ACR responses at month 4 in the final model based on the significance level of .001. The VPC showed that most of the responder rates observed in each C_{minss} quartile were within the prediction interval for each JIA-ACR response category (Figure 4). The cumulative probability (log odds) of response increased in proportion to log-transformed C_{minss}, and JIA-ACR30 rates approached a plateau when $C_{minss} \geq 10$ μg/mL (Figure 5). Compared with 10 mg/kg intravenous once-monthly dosing, abatacept weight-tiered subcutaneous weekly dosing provided a comparable and near-maximal efficacy response for JIA-ACR30 in month 4.

Discussion

This article is the first comprehensive characterization of intravenous and subcutaneous abatacept PK in patients with pJIA and the first to describe the abatacept E-R relationship in these patients.

Initially, a weight-normalized dose administered weekly was proposed and was expected to elicit a predicted exposure range for C_{minss} such that the majority of patients with pJIA would exhibit C_{minss} concentrations ≥ 10 μg/mL. Despite the inherent differences between weight-tiered and weight-normalized dosing regimens, the predicted distributions of C_{minss} associated with the proposed weight-tiered dosing regimen (Figure S3) were expected to be comparable to the predicted exposure associated with the weight-normalized dose in patients weighing ≥50 kg. However, the predicted distributions of C_{minss} associated with the proposed weight-tiered dosing regimen are expected to be overlapping in patients weighing 25 to < 50 kg and higher than the predicted exposure associated with the weight-normalized dose in patients weighing < 25 kg. The E-R safety analysis for subcutaneous abatacept in patients with RA demonstrated that higher C_{minss} did not result in a higher occurrence of infections.[15] Therefore, this inherent difference between weight-tiered and weight-normalized dosing is not expected to affect the safety profile in younger, lighter-weight patients with pJIA. The objective of the weight-tiered subcutaneous abatacept dosing regimen of 50, 87.5, and 125 mg administered weekly to patients with pJIA weighing < 25, 25 to < 50, and ≥ 50 kg, respectively, was to deliver abatacept C_{minss} concentrations of at least 10 μg/mL in > 90% of patients across all body weights throughout the age range of 2-17 years of age.

Results of the phase 3 study in patients with pJIA showed that the observed values for abatacept C_{minss} using the weight-tiered subcutaneous dosing regimen were higher than expected (Figure S5), and exposure targets for C_{minss} were achieved in > 99% of patients with pJIA. During dose selection for subcutaneous abatacept in pJIA patients, a population PK model was developed (Model 3) from existing models used for RA patients administered intravenous and subcutaneous abatacept (Model 2) and adult and pJIA patients administered intravenous abatacept (Model 1). Model 3 assumes that the absorption parameters in pediatric pJIA patients are the same as those used in adult patients with RA; results of the phase 3 study suggest that this assumption may not be valid. Although C_{minss} values observed with subcutaneous abatacept in this study were higher than with intravenous abatacept, the

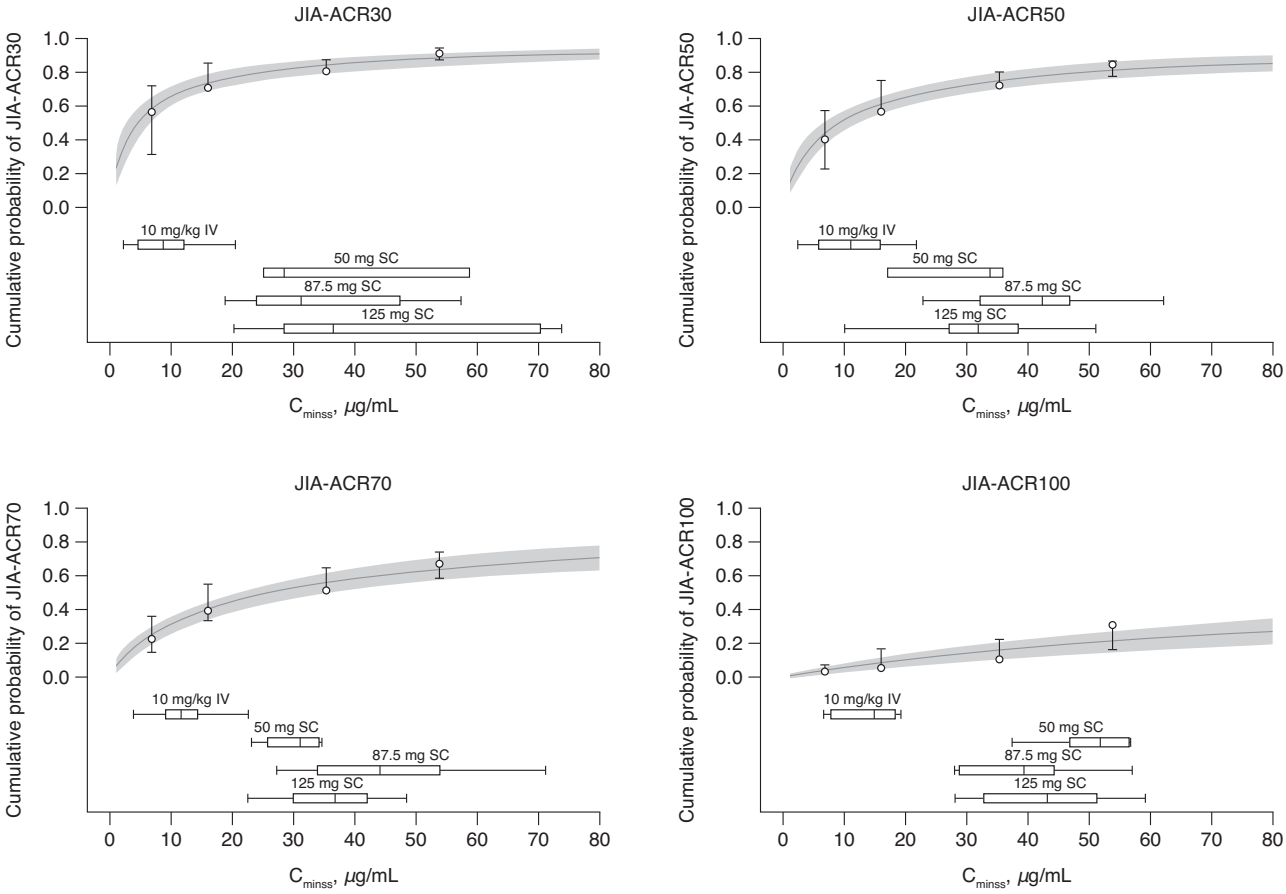

Figure 4. Visual predictive check of the final exposure-response JIA-ACR model. The vertical lines represent the 90% prediction interval of the observed probability of JIA-ACR response by quartiles of C_{minss}. Box plots of the distribution of simulated C_{minss} are at the bottom for each dosing regimen. ACR, American College of Rheumatology; C_{minss}, steady-state trough concentration; IV, intravenous; JIA, juvenile idiopathic arthritis; SC, subcutaneous.

weight-tiered subcutaneous dosing strategy provided a safe and well-tolerated route of abatacept administration for patients with pJIA, based on the safety and immunogenicity data reported.[14]

The final population PK model adequately described abatacept concentration-time profiles for patients with RA and those with pJIA. Body weight was the only covariate with a clinically relevant effect on abatacept exposure for both intravenous and subcutaneous administration. Higher body weight correlated with faster clearance and confirmed the importance of the weight-tiered dosing regimens.

Compared with the population PK model in patients with RA,[15] the inclusion of data from patients with pJIA resulted in a 41.5% increase in the KA, suggesting that the absorption of abatacept could be faster in patients with pJIA. In addition, the KA was 61.5% higher in this analysis than in the analysis of data for subcutaneous and intravenous abatacept that excluded patients aged 2 to < 6 years (data not shown), suggesting that abatacept could exhibit faster subcutaneous absorption and have a shorter absorption half-life in younger patients with pJIA. The difference between the KA estimates in the 2 pJIA populations (2-17 and 6-17 years old) could be because additional covariate effects, especially disease status, were incorporated in bioavailability (F) in the current model; therefore, the estimate for absorption-related parameter KA was affected.

In addition, this analysis showed that patients with pJIA generally exhibit higher (28% higher) absolute bioavailability for the subcutaneous formulation than patients with RA. After subcutaneous administration, fusion proteins such as abatacept are expected to enter systemic circulation mostly via convection into lymphatic vessels.[22] It has been reported that lymphatic flow increases with activity, heat, or massage.[22] The higher bioavailability of subcutaneous abatacept in patients with pJIA might be because of an increase in lymphatic transport of proteins because of a higher activity level in pediatric patients compared with adults. The difference in abatacept subcutaneous bioavailability between patients with pJIA and patients with RA

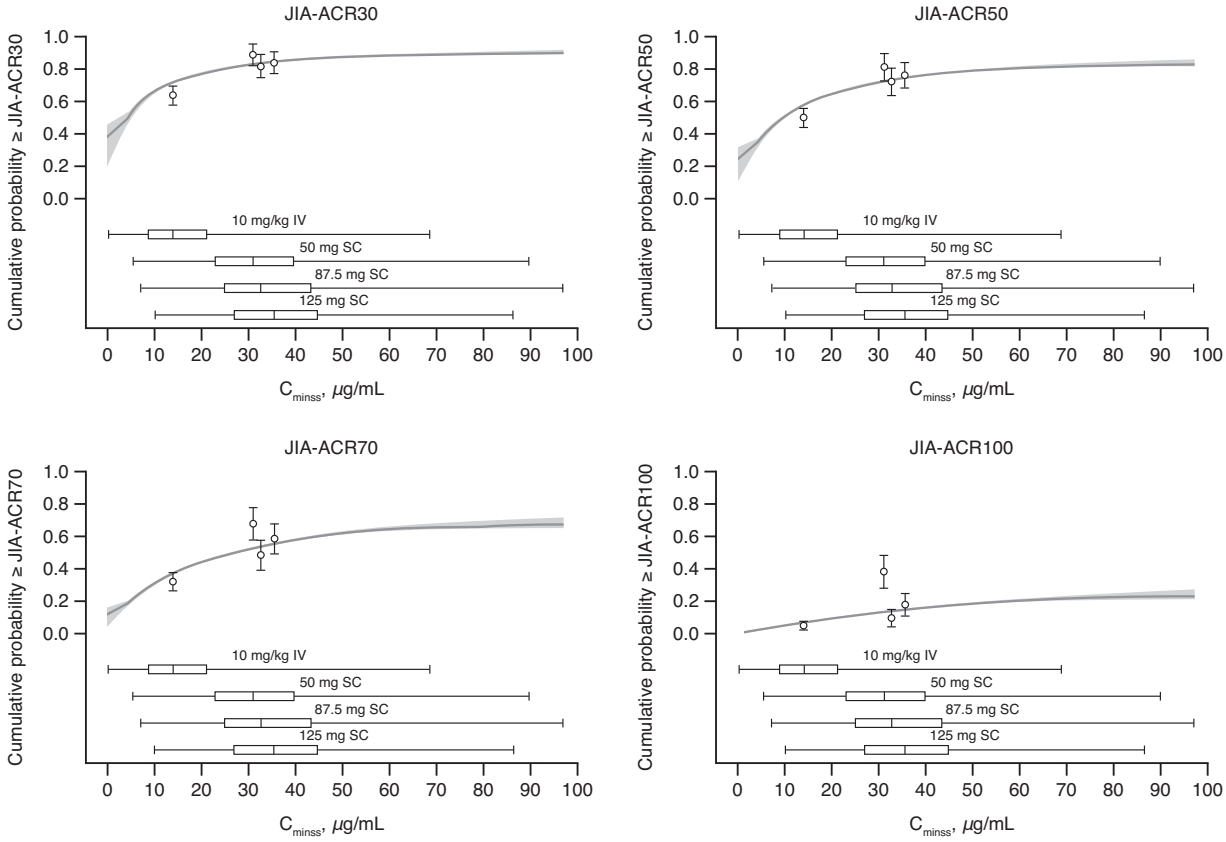

Figure 5. Cumulative probability of JIA-ACR response in month 4 versus C_{minss}. The solid line and shaded region represent the median and 90% prediction interval, respectively, of the cumulative probability ≥ JIAACR30/50/70/100. The symbols represent the observed proportion of patients ≥ JIAACR30/50/70/100 (90%CI). Boxes are 25th, 50th, and 75th percentiles; whiskers extend to the minimum and maximum values. ACR, American College of Rheumatology; C_{minss}, steady-state trough concentration; IV, intravenous; JIA, juvenile idiopathic arthritis; SC, subcutaneous.

may also be explained by the difference in neonatal Fc receptor (FcRn) expression/prevalence in children and adults in the subcutaneous injection area. Binding of monoclonal antibodies (mAbs) to FcRn and the role of this interaction in protecting mAbs from lysosomal catabolism and extending their biologic half-life is well established.[23,24] Therefore, it could be hypothesized that various mAbs (and Fc-fusion proteins such as abatacept) may exhibit similar absorption patterns because of structural resemblance. Binding to FcRn creates a depot that is protected from degradation, where only free mAbs can undergo presystemic elimination or be absorbed. Several studies have shown that binding to FcRn is an important determinant of subcutaneous absorption of mAbs. It was reported that the subcutaneous bioavailability of the monoclonal IgG1 antibody 7E3 was 3-fold higher in wild-type mice compared with FcRn-deficient animals.[25] The higher subcutaneous bioavailability of abatacept in pJIA might be because of more expression/prevalence of FcRn at the subcutaneous injection site in children than in adults, producing more FcRn-mediated protection of abatacept from proteolytic degradation in children. The covariate effects included in the final PK model were in agreement with both previous analyses.[15,18] Disease (pJIA vs RA) was not a significant covariate and is likely to have minimal impact on the PK of abatacept.

The population PK model adequately described the observed data and can be used to simulate C_{min} values for the E-R analysis. The CL parameter in the population PK model has greater impact on the estimate of C_{min} compared with VC, VP, F, and KA, and the shrinkage associated with the estimate of CL is small (< 15%). The model simulated C_{min} values should be relatively unaffected by shrinkage on VC, VP, F, and KA.

The E-R analysis indicated that a proportional odds model with a log-linear function of C_{minss} adequately described the E-R relationship for JIA-ACR responses following intravenous or subcutaneous dosing. C_{minss} was a statistically significant predictor of JIA-ACR responses at month 4. The probability of a JIA-ACR response at month 4 increased with increasing C_{minss}, but approached a plateau with JIA-ACR30 at $C_{minss} \geq 10$ μg/mL. Overall, there was good concordance between the predicted probability of response

and the observed response across the range of C_{minss} exposures.

The E-R analysis in patients with RA, along with the efficacy and safety results from the ACQUIRE trial,[5] demonstrated that the fixed-dose regimen of subcutaneous abatacept (125 mg weekly), and the monthly regimen of intravenous abatacept (body-tiered dose of 10 mg/kg monthly) were therapeutically equivalent for the treatment of RA. Similarly, the results of this analysis, along with the results of phase 3 trials in patients with pJIA[12–14] suggest that the weight-tiered subcutaneous abatacept dosing regimen is therapeutically equivalent to the intravenous dosing regimen for abatacept in pJIA. Abatacept exposure measurements at steady state in patients with pJIA were similar in each age group, suggesting that the weight-tiered subcutaneous and intravenous dose regimens[16] provide comparable exposures and therapeutic benefit across the age range of patients with pJIA.

The advantage of the weight-tiered abatacept dosing regimen is that it meets the requirements for an age-appropriate presentation while retaining the advantages of a weight-normalized dose in terms of the variability of C_{minss} across the wide range of weights found in pJIA. One potential weakness of the weight-normalized dose administration, whether by the intravenous or subcutaneous routes, is that the C_{minss} distribution is expected to decrease as weight decreases in patients with pJIA. This occurs with weight-normalized dose administration because weight-normalized clearance of abatacept increases as body weight decreases.

Conclusions

Evaluation of steady-state trough concentrations (C_{minss}) confirmed that a weight-tiered subcutaneous dosing strategy produced abatacept exposure above the threshold of ≥ 10 μg/mL associated with maximum efficacy. The final population PK model adequately described the abatacept PK data for patients with pJIA aged 2 to 17 years. Body weight was the only covariate with a clinically relevant effect on abatacept exposure. The proportional odds model with a log-linear function of C_{minss} adequately described the E-R relationship for JIA-ACR responses in patients with pJIA administered intravenously or subcutaneous abatacept. The weight-tiered subcutaneous abatacept dosing regimen provides near-maximal efficacy for JIA-ACR30 response and is therapeutically comparable to the intravenous dosing regimen for abatacept in pJIA.

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Conflicts of Interest

Y.G. was an employee of Bristol Myers Squibb at the time of the analysis. A.R. and B.M. are employees of and hold stock options and/or bond holdings in Bristol Myers Squibb. J.A.P. is an employee of and holds stock options and/or bond holdings in Cognigen Corporation, Buffalo, New York.

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Data Sharing

The Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

Author Contributions

All authors contributed to the writing of the article, designed and carried out the study research, analyzed the data, revised the work critically for important intellectual content, and agree to be accountable for all aspects of the work.

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