W-069

Population Pharmacokinetics and Exposure–Response Analyses for Abatacept in Juvenile Idiopathic Arthritis

Xiaohui Li,[1] *Julie A Passarell*,[2] *Kuan-ju Lin*,[2] *Amit Roy*,[1] *Bindu Murthy*,[1] *Ihab G Girgis*[1]

[1]*Bristol-Myers Squibb, Princeton, NJ, USA;* [2]*Cognigen Corporation, a SimulationsPlus Company, Buffalo, NY, USA*

Introduction

- Polyarticular-course juvenile idiopathic arthritis (pJIA) is the most common chronic rheumatic disorder in children and one of the leading causes of childhood-acquired disability.[1]
- Treatment with biologic (b)DMARDs is now well established, leading to improved clinical outcomes for patients with JIA.[2]
  - Abatacept has a mechanism of action that is fundamentally different from that of other bDMARDs, with a proven efficacy and safety profile in pJIA.[2]
- Abatacept, a selective T-cell co-stimulation modulator, is approved for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) and can be administered as either weight-tiered IV (~10 mg/kg/month) or fixed-dose SC (125 mg/week) dosing.[3]
  - The exposure–response (E–R) relationship established in JIA and adult RA has demonstrated that a steady-state trough concentration (C_{minss}) threshold of 10 µg/mL provides a near-maximal efficacy response.
- In addition, abatacept was approved in the US in 2008 (IV formulation; 10 mg/kg monthly) for use in pediatric patients aged ≥6 years with moderately to severely active pJIA.[4]
- In 2017, based on the analyses presented herein, the weight-tiered SC dosing (10–<25 kg, 50 mg; 25–<50 kg, 87.5 mg; ≥50 kg, 125 mg/week) received approval in the US for use in children aged ≥2 years with moderately to severely active pJIA.[3]

Objectives

- Population pharmacokinetics (PPK) and efficacy E–R analyses of abatacept were conducted to determine whether the proposed weight-tiered SC regimen[5] provided near-maximal efficacy by achieving the target exposure and was therapeutically comparable to the IV 10 mg/kg/month regimen in patients with pJIA.

Methods

- Combined data from studies with IV or SC abatacept were analyzed to assess clinically relevant exposure outcome measures applicable to both formulations.
- The PPK model was developed with data from 13 Phase II/III studies in RA (11 studies; n=2213) and pJIA (patients aged 2–17 years; 2 studies; n=389). A similar PPK analysis was conducted with data for the cohort of 2–5-year-old patients with pJIA excluded (data not shown).
- The E–R model for the American College of Rheumatology pediatric scores (pJIA-ACR30/50/70/100 responses as an ordered categorical efficacy endpoint) at Month 4 was developed with data from two Phase III studies in patients with pJIA (aged 6–17 years; n=357) for whom summary measures of abatacept exposure determined by the PPK analysis that excluded the 2–5 year pJIA data were available.
- Predefined relevant covariates investigated in the PPK and E–R analyses were:

PPK analysis

- Continuous covariates at baseline: age, body weight, albumin, calculated glomerular filtration rate, serum creatinine, total bilirubin, tender joint count (TJC) and swollen joint count (SJC).
- Categorical covariates: sex (male vs female), race (white vs non-white), disease (JIA vs RA), baseline disease duration (≤2, 2–5, >5–10 and >10 years), methotrexate (MTX) use (yes vs no) at baseline, corticosteroid use (yes vs no) and NSAID use (yes vs no) at baseline.

E–R analysis

- Continuous covariates at baseline: age, body weight, TJC, SJC, C-reactive protein and Physician Global Assessment of disease activity.
- Categorical covariates: sex (male vs female), race (white vs non-white), administration (SC vs IV), prior anti-tumor necrosis factor-α use (yes vs no), JIA category (persistent oligoarthritis, systemic arthritis, and all other subtypes vs polyarticular rheumatoid factor [RF]+ and polyarticular RF–), immunogenicity (positive vs negative), baseline MTX use (yes vs no), corticosteroid use (yes vs no) at baseline, NSAID use (yes vs no) at baseline and disease duration (≤2, 2–5, >5–10 and >10 years).

- In the E–R analysis, PPK model-predicted exposures were: steady-state peak, trough and time-averaged concentrations.
- Both the PPK and E–R models were evaluated using visual predictive checks (VPC).
- Stochastic simulations were performed using the final PPK and E–R models to simulate expected distributions of abatacept exposure measures and the probability of JIA-ACR response at 4 months.

Results

PPK analysis

- A total of 12,226 (73.5%) samples were included in the PPK analysis, 129 of which were from patients aged 2–5 years.
- Abatacept PK were characterized by a linear two-compartment model with either zero-order IV infusion or first-order SC absorption, and first-order elimination (Table 1).
- Baseline body weight was the only significant covariate considered to have a clinically relevant impact on abatacept exposure. Age and sex (corrected for body weight) and concomitant medications (including MTX, corticosteroids and NSAIDs) did not influence abatacept clearance (Figure 1).
- The prediction-corrected VPC showed that ~90% of the observed abatacept concentrations were within the 90% prediction interval range (Figure 2).
- SC weight-tiered abatacept doses achieved C_{minss} that exceeded the target exposure for near-maximal efficacy (C_{minss} ≥10 µg/mL).

E–R analysis

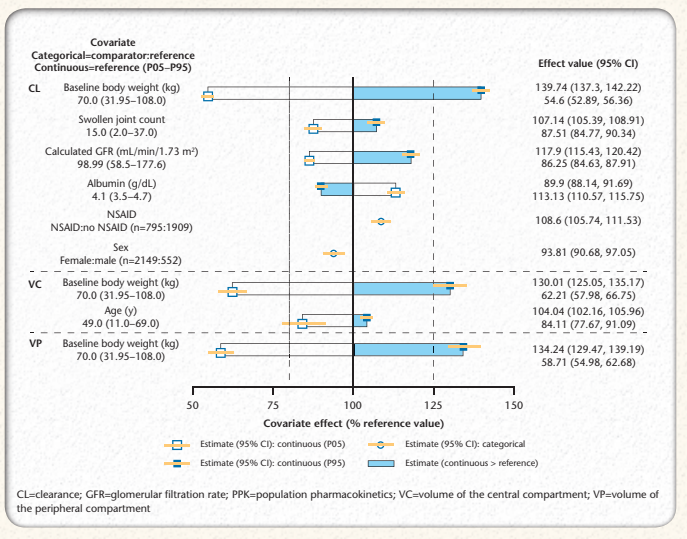
- A total of 357 (91.8%) patients aged 6–17 years were included in the E–R analysis.
- C_{minss} was the best measure for predicting the JIA-ACR response using a proportional odds model.
- The final JIA-ACR model was a proportional odds model with a log linear function of C_{minss} for both IV and SC administration. Final parameter estimates are presented in Table 2.
- No covariates were significant predictors of the probability of a JIA-ACR response at Month 4.
- The VPC showed that the majority of the observed proportions of responders in each quartile of C_{minss} fell within the prediction interval for each JIA-ACR response category (Figure 3).
- The cumulative probability (log odds) of response increased in proportion to log-transformed C_{minss}, and JIA-ACR30 approached a plateau for C_{minss} ≥10 µg/mL (Figure 4).
- Compared with 10 mg/kg IV once-monthly dosing, abatacept weight-tiered SC weekly dosing provided a comparable and approaching maximal response for JIA-ACR30 at Month 4.

Table 1. Parameter Estimates of the Final PPK Model Fitted to Expanded Dataset of RA and JIA Studies Including Data From the 2–5 Years Cohort

Parameter	Final parameter estimate		Inter-individual variability/ residual variability	
	Typical value	%RSE	Estimate	%RSE
Absorption rate constant, L/h	0.00898	14.6	0.732	40.2
VC, L	3.36	1.49	0.0504	15.0
Power of weight on VC	0.605	7.57		
Power of age on VC	0.116	23.5		
CL, L/h	0.0200	2.07	0.0642	5.45
Power of weight on CL	0.772	2.68		
Power of GFR on CL	0.282	6.57		
Power of albumin on CL	–0.780	9.46		
Power of SJC on CL	0.0797	12.2		
Exponent of NSAID on CL	0.0825	16.5		
Exponent of female sex on CL	–0.0639	27.1		
VP, L	4.05	4.46	0.184	14.6
Power of weight on VP	0.679	6.27		
Intercompartmental CL, L/h*	0.0269	8.40	NE	NA
Bioavailability of SC formulation	1.63	7.42	0.818	19.9
Proportional residual error	NA	NA	0.0553	3.28
Additive residual error	NA	NA	0.00165	53.8
Minimum value of the objective function=61,162.245				

*Absolute bioavailability = 1 / [1 + exp (–1.63–0.818)] = 92.04%
CL=clearance; GFR=glomerular filtration rate; NA=not applicable; NE=not estimated; PKK=population pharmacokinetics; RSE=relative standard error; SJC=swollen joint count; VC=volume of the central compartment; VP=volume of the peripheral compartment

Figure 1. Covariate Effect Forest Plot Based on Final PPK Model



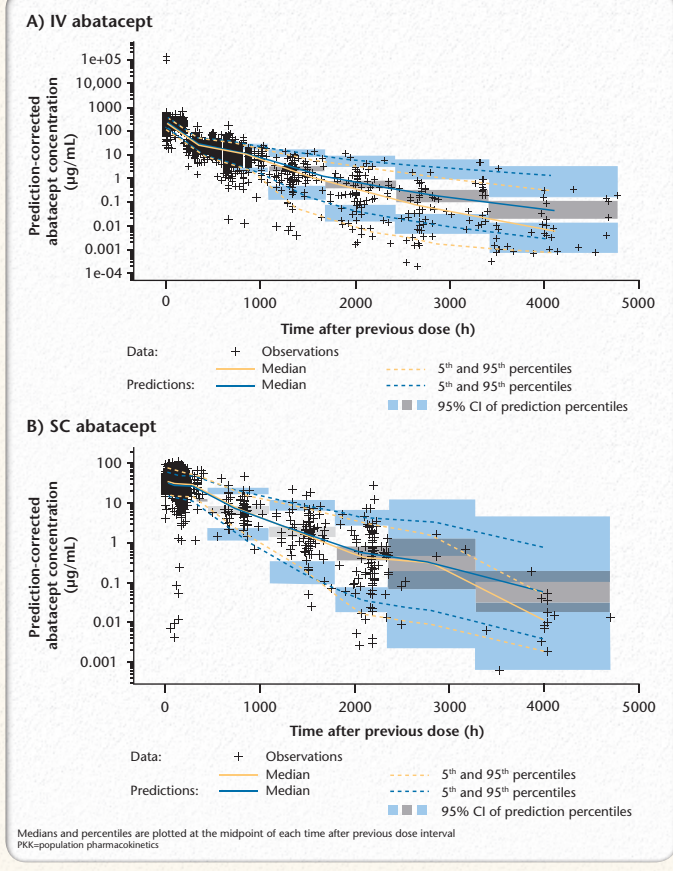
CL=clearance; GFR=glomerular filtration rate; PPK=population pharmacokinetics; VC=volume of the central compartment; VP=volume of the peripheral compartment

Table 2. Parameter Estimates of the Final Model for Probability of JIA-ACR Response

Parameter	Estimate (RSE%)
Intercept for JIA-ACR30 (logit)	1.13 (11.2)
Intercept for JIA-ACR50 (logit)	–0.598 (14.3)
Intercept for JIA-ACR70 (logit)	–0.794 (11.6)
Intercept for JIA-ACR100 (logit)	–2.03 (8.78)
Slope for log(C_{minss}) (1/[ug/mL])	0.678 (16.4)
Minimum value of the objective function=1039.4	

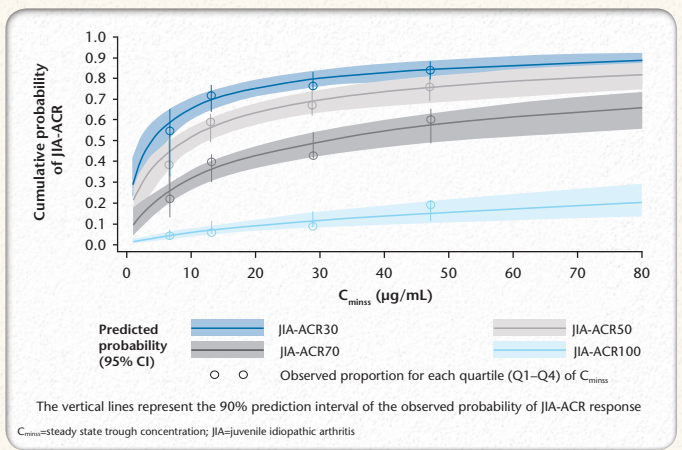
C_{minss}=steady state trough concentration; JIA=juvenile idiopathic arthritis; RSE=relative standard error

Figure 2. Prediction-Corrected Visual Predictive Check of the Final PPK Model



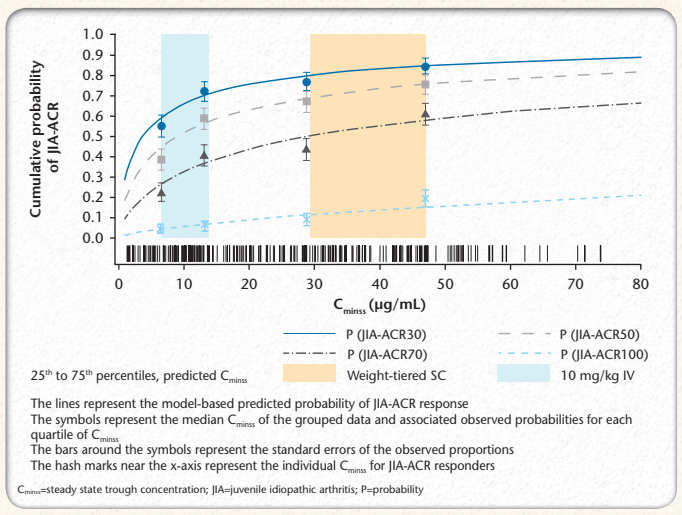
Medians and percentiles are plotted at the midpoint of each time after previous dose interval
PKK=population pharmacokinetics

Figure 3. Visual Predictive Check of the Final JIA-ACR Model



The vertical lines represent the 90% prediction interval of the observed probability of JIA-ACR response
C_{minss}=steady state trough concentration; JIA=juvenile idiopathic arthritis

Figure 4. Cumulative Probability of JIA-ACR Response at Month 4 Versus C_{minss}



The lines represent the model-based predicted probability of JIA-ACR response
The symbols represent the median C_{minss} of the grouped data and associated observed probabilities for each quartile of C_{minss}
The bars around the symbols represent the standard errors of the observed proportions
The hash marks near the x-axis represent the individual C_{minss} for JIA-ACR responders

C_{minss}=steady state trough concentration; JIA=juvenile idiopathic arthritis; P=probability

Conclusions

- The final PPK model adequately described abatacept concentration–time profiles for patients with RA and those with pJIA (including patients aged 2–17 years).
- A proportional odds model with a log linear function of C_{minss} adequately described the E–R relationship for JIA-ACR in patients with pJIA administered IV or SC abatacept.
- The PPK and E–R analyses demonstrated that the proposed weight-tiered SC abatacept dosing regimen provides near-maximal efficacy (JIA-ACR30) by achieving the target exposure of C_{minss} ≥10 µg/mL and is therapeutically comparable to the IV abatacept regimen in pJIA.

References

1. Beukelman T, et al. *Pediatr Rheumatol Online J* 2017;**15**:30, doi:10.1186/s12969-017-0160-6.
2. Stoll ML, Cron, RQ. *Pediatr Rheumatol Online J* 2014;**12**:13, doi: 10.1186/1546-0096-12-13.
3. Bristol-Myers Squibb. Orencia (abatacept) US prescribing information. Available at: http://packageinserts.bms.com/pi/pi_orencia.pdf. Last updated 2017. Accessed August 1, 2017.
4. Ruperto N, et al. *Lancet* 2008;**372**:383–91.
5. Li X, et al. ACoP 2016, Bellevue, WA.

Acknowledgments

This study was sponsored by Bristol-Myers Squibb. Professional medical writing and editorial assistance was provided by Claire Line, PhD, at Caudex and was funded by Bristol-Myers Squibb.

Disclosures

XL, AR, BM, and IGG: employees of, and hold stock options and/or bond holdings in, Bristol-Myers Squibb. JAP and KL: employees of, and hold stock options and/or bond holdings in, Cognigen Corporation, a SimulationsPlus Company, Buffalo, NY.