The Journal of Clinical Pharmacology
54(11) 1230–1238

DOI: 10.1002/jcph.334

Population Pharmacokinetics of Brodalumab in Healthy Adults and Adults With Psoriasis From Single and Multiple Dose Studies

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Abstract

Brodalumab, a human monoclonal IgG2-antibody, acts as a potent antagonist at the interleukin-17 receptor A, which is important in the pathogenesis of psoriasis. To characterize the pharmacokinetics of brodalumab and assess the effects of covariates, brodalumab concentrations from Phase 1a and Phase 2 clinical studies in healthy adults and subjects with psoriasis were used to construct a population PK model. The final two-compartment model with parallel linear and non-linear elimination pathways fit the data well. The population typical values for PK parameters CL, V, and V_{max} were 0.223 L/day, 4.62 L, and 5.40 mg/day with between-subject-variability of 69.2, 69.6, and 25.9%CV, respectively. Body weight (BW) was an important covariate on CL (and Q), V (and V_2) and V_{max}, with estimated effect exponents of 0.598, 0.849, and 1.12, respectively. Based on simulations from the final model, for doses between 140 and 210 mg, AUC was predicted to be greater than two fold higher in subjects weighing less than 75 kg compared to reference subjects. Age and diagnosis had smaller influence on exposure and was not clinically significant. These data suggest that BW is an important covariate explaining some of the variability in population PK observed in human clinical trials with brodalumab.

Keywords

interleukin 17 receptor, brodalumab, monoclonal antibody, population pharmacokinetics, psoriasis

Psoriasis is a chronic inflammatory dermatological disease that is estimated to affect about 2–4% of the world's population, although the prevalence varies widely among geographic areas and races.[1,2] The most common form of psoriasis presents as plaque-type psoriasis with recurrent exacerbations and remissions of thickened, erythematous, scaly patches of skin due to hyperproliferation of keratinocytes and is characterized by infiltration of inflammatory cells. Psoriatic arthritis, a chronic inflammatory disorder that involves joints, tendon sheaths, the axial skeleton as well as skin and nails, has an estimated prevalence of 30% among patients with psoriasis.[3]

Although the exact pathogenesis of psoriasis and psoriatic arthritis has not been fully determined, emerging data from genetic and expression studies have pointed to the important role of the pro-inflammatory cytokine interleukin-17 (IL-17), and the leukocyte populations that produce this cytokine, including the Th17 subset of T helper cells.[4] Besides in the pathogenesis of psoriasis, IL-17 has also been implicated to contribute to numerous other inflammatory autoimmune diseases such as asthma and chronic obstructive pulmonary disease (COPD).[5–7]

The IL-17 family comprises six cytokines, IL-17A through IL-17F, that bind to a total of five receptors (IL-17RA through IL-17RE).[4,8] Increased expression of IL-17A, IL-17C, and IL17F has been demonstrated in psoriatic lesions.[9–11] Furthermore, IL-17 levels in patients with plaque psoriasis was positively correlated with the Psoriasis Area and Severity Index (PASI) score, a clinical measurement for the severity of psoriasis commonly used in clinical trials.[11] Except for IL-17RA for which comparable expression has been reported in lesional and non-lesional psoriatric skin, expression of other IL-17 receptor members was significantly down-regulated in psoriatic lesional skin.[9]

Brodalumab (formerly known as AMG 827) is a human, Chinese hamster ovary (CHO) cell-derived immunoglobulin G2 (IgG2) monoclonal antibody that inhibits the biologic activity of IL-17A, IL-17F, IL-25 (IL-17E) homodimers and the IL-17A/F heterodimer by binding to IL-17RA with high affinity and thus blocking

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Submitted for publication 2 April 2014; accepted 19 May 2014.

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the inflammatory downstream activity of the IL-17 receptor cascade in the skin. Recent results of randomized, double-blind, placebo-controlled phase 1 and 2 studies in patients with moderate to severe psoriasis revealed that brodalumab significantly improved plaque psoriasis as measured by the PASI score.[12,13] The phase 1 population pharmacokinetics and PK/PD relationship of brodalumab in healthy volunteers and psoriasis patients were recently characterized.[14] In the current manuscript, the objectives were (1) to extend the characterization of the pharmacokinetics of brodalumab using a population-based approach, (2) to estimate the magnitude of between-subject variability in pharmacokinetic parameters, and (3) to identify factors that contribute to the variability of PK parameters in subjects with moderate to severe plaque psoriasis.

Methods

Study Design and Subjects

Brodalumab serum concentration–time data for the current were obtained from two clinical trials evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of brodalumab in adult male and female subjects with moderate to severe psoriasis and healthy volunteers (www.clinicaltrials.gov #NCT00867100 and #NCT00975637). Both studies were performed in accordance with the ethical principles set forth in the Declaration of Helsinki and its revisions, the International Conference on Harmonization (ICH) E6 Guidance for Good Clinical Practice (CPMP/ICH/135/95) and all other applicable regulatory requirements and standard operating procedures (SOPs), and study protocols underwent IRB review at the clinical sites.

The first study (#NCT00867100) was a two-part, multi-center, randomized, double-blind, placebo-controlled first-in-human single ascending dose study (Phase 1a study) in healthy volunteers (Part A) and subjects with moderate to severe psoriasis (Part B). In part A, 57 healthy volunteers were randomly assigned to receive a single SC dose of 7 mg (n = 6), 21 mg (n = 6), 70 mg (n = 6), 210 mg (n = 6), or 420 mg (n = 6) brodalumab or a single IV dose of 21 mg (n = 3), 210 mg (n = 4) or 700 mg (n = 6) brodalumab or placebo (n = 14). In part B, 25 subjects with psoriasis received a single dose of placebo (n = 5), or brodalumab at dosages of 140 mg SC (n = 4), 350 mg SC (n = 8), or 700 mg IV (n = 8). All IV doses were administered as a 30 min infusion. The primary results and population PK/PD from this study have been previously reported.[12,14]

The second study (#NCT00975637) was a Phase 2 multi-center, randomized, double-blind, placebo-controlled multiple dose study (Phase 2 study) in patients with moderate to severe psoriasis as described previously.[13] In this study, approximately 24% were co-morbid with psoriatic arthritis. A total of 197 subjects were enrolled and administered placebo or brodalumab at a dose of 70, 140, or 210 mg SC at day 1, and on weeks 1, 2, 4, 6, 8, and 10 or 280 mg SC on day 1, and weeks 4 and 8 at a 1:1:1:1:1 ratio.

Drug Administration

Brodalumab was manufactured by expression in Chinese hamster ovary (CHO) cells and packaged at Amgen, Inc. (Thousand Oaks, CA, USA). Brodalumab was formulated at 70 mg/mL in 10 mM acetate, 9.0 (w/v)% sucrose, 0.004% (w/v) polysorbate 20 at pH 5.2; placebo (matching vehicle control) was formulated with the same excipients. The investigational product and placebo were supplied as sterile 1-ml fill in clear 5 mL glass vials, stored at −20°C to −70°C in a non-frost-free freezer, until ready for SC or IV administrations.

In the phase 1a study, SC doses were administered to the subject's anterior abdominal wall; for individual SC doses exceeding 1.5 ml, the dose was split into separate syringes and administered into different sites on the subject's anterior abdominal wall laying at least 2 cm apart and with no more than 30 seconds between each injection. Four doses were administered as 30-minute infusion in a volume of 100 mL in sterile 5% dextrose using a peristaltic infusion pump. Before and after each IV infusion, the IV access was flushed with 5% dextrose.

SC doses in the phase 2 study were administered into the anterior upper abdomen, thigh or upper arm, with each injection administered at a different site. Irrespective of the treatment arms, all subjects received four single SC injections at day 1 and weeks 4 and 8 and three single SC injections at weeks 1, 2, 6, and 10.

Sample Collection and Analysis

In study part A of the phase 1a study, blood samples for determination of brodalumab serum concentrations were collected pre-dose, 0.5, 4, 8, 24 hours post-dose and on days 1, 2, 3, 4, 7, 11, 14, 21, 28, and 42. Additional blood samples were obtained on day 63 in the ≥210 mg dose cohorts. Subjects receiving IV brodalumab had an additional sampling time point at the end of the 30-min IV infusion. In part B, blood samples were collected pre-dose, 0.5, 2, 4, and 8 hours post-dose and 2, 7, 14, 28, 42, 63, and 85 days after brodalumab administration.

In the phase 2 study, blood samples were obtained on study days 14, 28, 56, 84, and 112 as trough samples for all subjects. A subset of 44 patients underwent intensive sampling with additional blood samples drawn on study days 7 (pre-dose), 9, 59, 63, and 70 (pre-dose).

Blood samples (~5 mL) for pharmacokinetic analysis were collected into red-top Vacutainer™ tubes without additives or anticoagulants to allow for serum preparation. Samples were allowed to coagulate for at least 30 minutes at room temperature. Within 1 hour of

collection, samples were centrifuged at 2000*g* for 15 min, serum was aliquoted into polypropylene cryovials and stored frozen at −70°C in non-frost-free freezer until analysis.

Brodalumab concentrations were quantified using a validated enzyme-linked immunosorbent assay method with a lower limit of quantification of 0.05 μg/mL.

Population Pharmacokinetic Analysis

Population pharmacokinetic analysis was performed using NONMEM software version 7[15] with the gfortran FORTRAN compiler. The Iterative Two-Stage (ITS) method, followed by the Stochastic Approximation Expectation Maximization (SAEM) method, followed by Monte Carlo Importance Sampling (IMP) method was used for structural and covariate model development during the population PK analysis. The SAEM method was conducted in two phases: (i) burn-in phase, followed by (ii) accumulation phase. The IMP method was evaluated using the EONLY = 1 ("evaluation only") option with sufficient number of iterations to provide a stationary objective function for the purpose of obtaining standard error estimates for each parameter.

For population PK analysis, subjects with at least one brodalumab serum concentration above the LLOQ were included in the analysis. For the purposes of simulation (eg, posterior-predictive checks), all subjects enrolled in the trials were included in the analysis.

Following visual inspection of the concentration–time profiles, a two-compartment model with parallel linear and non-linear pathways was chosen as the structural model for the analysis. The ADVAN6 subroutine in the PREDPP library was used, which was parameterized in terms of linear (CL), and nonlinear (V_{max}, K_m) elimination, central (V) and peripheral (V_2) distribution volumes, inter-compartmental clearance (Q), and a first order absorption rate constant (K_a). Subcutaneous bioavailability (F) was fixed to 57.6% based on estimation of Phase 1 data.[14]

Because of the frequency of data below the LLOQ, indicators of observed data below LLOQ were included in the analysis, and data were modeled using an adjusted likelihood function (so called "M3 method"), which maximizes the likelihood of the data above the LLOQ, and treats the BQL data as censored.[16]

A log-normal model was used to describe the between-subject-variability (BSV) in the model parameter estimates:

$$P_i = TVP \times \exp(\eta_i)$$

where P_i is the individual model parameter for the ith subject, TVP is the typical value of the parameter value P, and η_i is the individual realization of a normally distributed random variable with mean zero and variance ω^2.

BSV was implemented as a full-block covariance matrix for random effects associated with the parameters for CL, V, V_{max}, K_a and V_2. The BSV of Q was fixed to an arbitrarily small value (15% CV) to allow the expectation maximization estimation method to efficiently move the parameter estimate for Q.[15] The variance estimates were presented as coefficients of variation (%CV).

The residual variability model was a combination of additive and proportional components:

$$Y = F(1 + \varepsilon_{1,i,j}) + \varepsilon_{2,i,j}$$

where Y is the observed concentration of brodalumab and F the modeled concentration, and $\epsilon_{1,ij}$ and $\epsilon_{2,ij}$ are realizations of normally distributed random variables with means of 0 and variances σ_1^2, and σ_2^2, respectively for the j^{th} time point for the i^{th} subject.

A full model approach was used to evaluate the significance of potential covariates in the final model.[17–19] Covariates explored included total body weight (TBW), age, gender and disease status (healthy volunteer or psoriasis). Height, BMI and BSA were excluded from covariate exploration due to their correlation to TBW.

Continuous covariates (COV) were normalized to a reference value (COV_{ref}; approximately population mean) and included into the model using a power function as shown in the following equation:

$$TVP = \theta_1 \left(\frac{COV}{COV_{ref}}\right)\theta^2$$

where TVP is the typical value of the model parameter for a subject with covariate COV, θ_1 is the typical value of the model parameter for a subject with covariate COV_{ref}, and θ_2 represents the effect exponent and thus provides an estimate of the magnitude of the covariate–parameter relationship.

The covariate effect exponents of TBW on central and inter-compartmental clearance (CL and Q) were assumed identical. Similarly, the covariate effect exponents of TBW on central and peripheral volume (V and V_2) were assumed identical.

For categorical covariates, the effect on PK parameters was modeled as a fraction (θ_2) relative to the reference group and implemented in the model as follows:

$$TVP = \theta_1 \times \theta_2^{IND}$$

where θ_1 represents the typical parameter estimate for subjects in the reference category (IND = 0).

Model Validation and Simulation

The performance of the final population PK model was evaluated using diagnostic plots and visual predictive checks. Additionally, the shrinkage of empirical Bayes

estimates of individual PK parameters was evaluated. To evaluate the impact of key covariates on the typical expected area under the concentration–time curve and maximum serum brodalumab concentrations at steady state, 1000 data sets were simulated using 1000 sets of population parameters sampled from the multivariate normal distribution using the simpar() functionality of the metrumrg (Metrum Research Group, LLC, Tariffville, CT, USA) R package.[20] To assess the impact of key covariates and uncertainty in the impact, simulations were based on the full covariate population PK structural model and estimated variance-covariance of parameter estimates, but excluding between-subject and residual variability. Each of the simulated data sets included a reference patient (40-year-old psoriasis patient with a body weight of 90 kg) and several patients where one of the covariates, age, TBW, or diagnosis, were modified. Summary statistics for the effect of the covariate on AUC and C_{max} relative to the reference subject are reported.

Results

A total of 1526 serum samples from 196 subjects (652 serum samples from 54 subjects in the phase 1a study and 874 serum samples from 142 subjects in the phase 2 study) were included the population PK analysis. Subject characteristics and demographic information are summarized in Table 1. A slightly higher median age and TBW were observed in the phase 2 study, which might be due to higher age and weight observed in patients with psoriasis and psoriatic arthritis (Supplemental Figure S1). Furthermore, a lower percentage of male subjects was present in the phase 2 study. All other demographic parameters were comparable between both studies. The correlation between selected demographics was explored graphically (Supplemental Figure S2). As expected, the measures of body size itself exhibited varying degrees of correlation with one another: total body weight (TBW) exhibited strong correlation with height (HT, $R^2 = 0.38$), body mass index (BMI, $R^2 = 0.88$), and body surface area (BSA, $R^2 = 0.98$).

Population PK Base Model

The structural two-compartment model with parallel linear and non-linear elimination from the central compartment adequately described the serum concentration–time profiles of brodalumab. The summary of brodalumab population PK parameter estimates is given in Table 2; a summary of variance and covariance for between-subject-variability is provided in Supplemental Table S1. The population typical values for the pharmacokinetic parameters clearance (CL), volume (V), and V_{max} were 0.226 L/day (SE: 0.86%), 3.89 L (SE: 1.0%), and 5.16 mg/day (SE: 2.0%) respectively. K_m was difficult to estimate using the available data and was fixed to 0.02 μg/mL based on an informal sensitivity analysis and the assay LLOQ (0.05 μg/mL). The validity of this approach was supported by the observation that the PK parameter estimates and overall model fit were not sensitive to the selection of K_m in the range of 0.01 and 0.1 μg/mL. The goodness-of-fit plots (Figure 1) for the base population PK model suggest that there was a good agreement between the observed and model predicted brodalumab concentrations and there was considerable unexplained variability (Figure 1). The between-subject variability (BSV) on CL, V, and V_{max} were 54.6, 84.2, and 37.8%CV respectively. Precision of the diagonal elements of the BSV estimates was 22% SE or less. As often observed, CL and V were highly correlated. Parameter

Table 2. Summary of Brodalumab Parameter Estimates of the Base Population PK Model

Parameters	Parameter Estimate (%SE)	BSV %CV (%SE)
CL (L/day)	0.226 (0.86%)	54.6% (22%)
V (L)	3.89 (1.0%)	84.2% (18%)
V_{max} (mg/day)	5.16 (2.0%)	37.8% (12%)
K_m (fixed) (μg/mL)	0.02	—
K_a (day^{-1})	0.243 (1.2%)	39.1 (19%)
Q (L/day)	0.820 (5.0%)	15% (fixed)
V_2 (L)	2.68 (1.3%)	56.5% (14%)
F (fixed) (%)	57.6	—
σ_1 (additive) (μg/mL)	0.421 (8.7%)	—
σ_2 (proportional) (%)	11.5 (5.0%)	—

BSV, between-subject variability; CL, clearance; F, subcutaneous bioavailability; K_a, absorption rate constant; K_m, Michaelis–Menten constant; V, volume of central compartment; V_2, volume of peripheral compartment, V_{max}, maximal velocity for nonlinear elimination; Q, intercompartmental transfer clearance; %SE determined by NONMEM covariance step after importance sampling.

Table 1. Demographics and Distribution of Covariates for Healthy Volunteers and Psoriasis Subjects Used for Population PK Modeling

Study	N	Mean (Median), Range					Gender, N (%Male)	Diagnosis HV/PSO, N (%HV)
		Age (Years)	TBW (kg)	Height (cm)	BMI ($kg\,m^{-2}$)	BSA (m^2)		
20060279	54	30.0 (25), 18–55	82.4 (79.6), 52.6–133.8	177 (177.5), 158–192	26.3 (24.7), 18.5–50.4	2.00 (1.98), 1.57–2.46	50 (92.6)	34 (63)
20090062	140	42.4 (41), 21–70	88.9 (87.1), 45–144.1	172 (172.8), 147.5–204	29.9 (29.2), 17.6–49.0	2.05 (2.07), 1.39–2.79	93 (66.4)	0 (0)
Combined	194	38.9 (39), 18–70	87.1 (86.1), 45–144.1	174 (175), 147.5–204	28.9 (27.9), 17.6–50.4	2.04 (2.04), 1.39–2.79	143 (73.7)	34 (17.5)

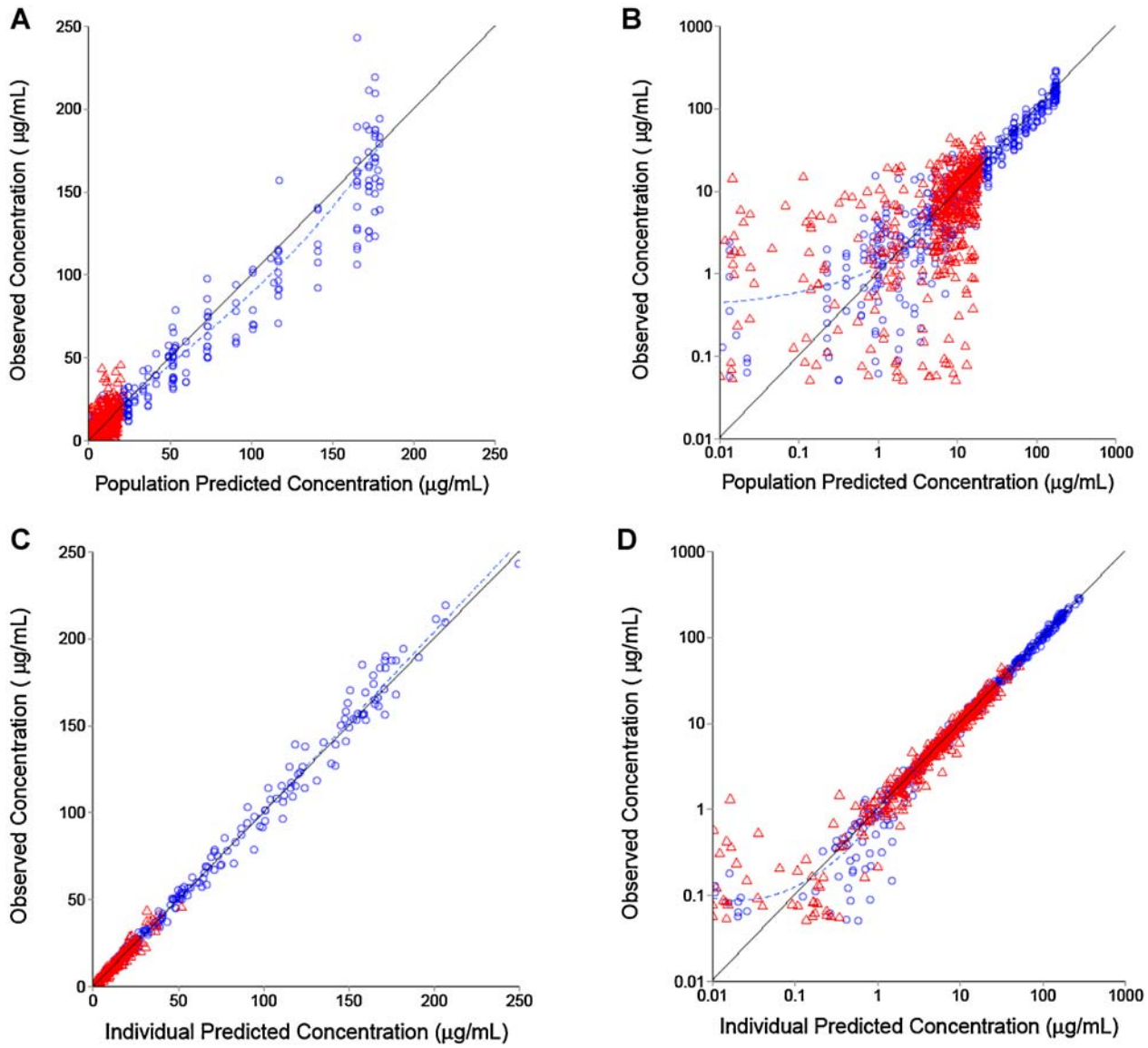

Figure 1. Goodness-of-fit plot for the base model. The black solid line represents the line of identity; the dashed blue lines represent the Loess curves. (A: linear-linear scale, B: log-log-scale) Population predicted versus observed brodalumab concentrations. (C: linear–linear scale, D: log–log scale) Individual predicted versus observed brodalumab concentrations. Blue circles represent data from phase 1a study, red triangles represent data from phase 2 study. Separate log–log and linear–linear scales are provided for the individual (A and B) and population (C and D) diagnostic plots because of the large range in the axes scales.

covariances were generally well estimated and the estimated shrinkage for all estimated individual random effect parameters was less than 26%.

To assess the predictive performance of the base population PK model, visual predictive checks were performed using model simulations and observed concentration data from Phase 1a and Phase 2 study. As shown in Figure 2 the majority of observed data were within the 80% or 90% prediction interval, respectively. The base population PK model also predicted well the percentage of subjects with brodalumab concentration below the LLOQ (Supplemental Figure S3).

Full Covariate Population PK Model

To develop a full covariate population PK model, potentially significant covariates were selected a priori based on clinical interest and plausibility, with an effort to eliminate co-linearity in predictors. Due to the high correlation observed between TBW, BMI, and BSA (Supplemental Figure S1), only TBW as a representation of body size was included into the full covariate model. Other covariates selected for inclusion in the final model included age and disease status (healthy volunteer or psoriasis).

The final population pharmacokinetic model described the serum concentration–time profile of brodalumab well.

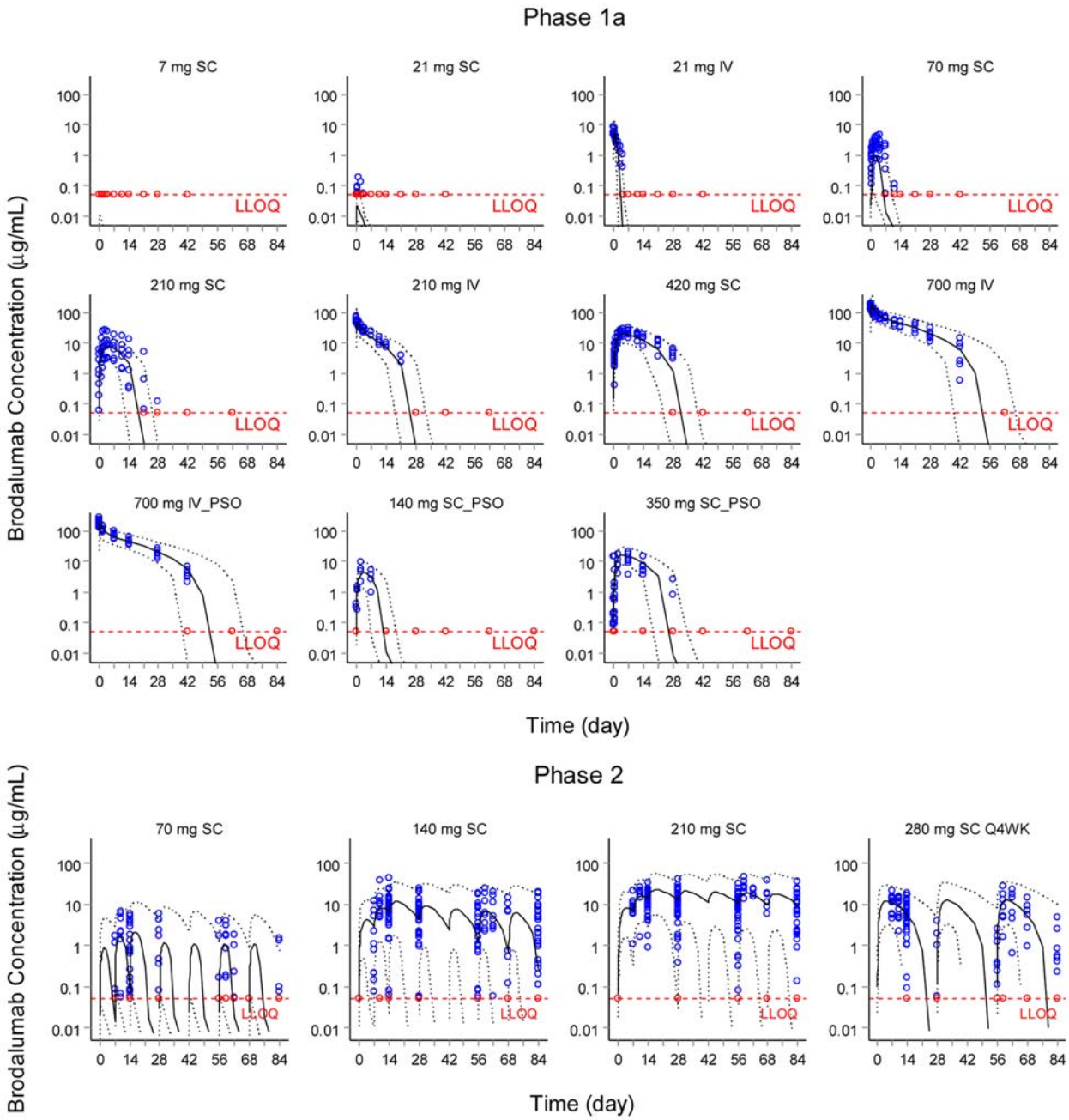

Figure 2. Visual predictive check of observed and model predicted serum brodalumab concentrations using the base model. Dashed horizontal red lines represent the LLOQ of 0.05 µg/mL. The 80% prediction interval (10^{th}–90^{th} percentile) for the Phase 1a study and the 90% prediction interval (5^{th}–95^{th} percentile) for the Phase 2 study are plotted (dashed lines). For both studies, the predicted median (50^{th} percentile) of the simulated brodalumab concentrations is symbolized by the solid line. Symbols represent the observed individual brodalumab concentrations.

The population typical values for the pharmacokinetic parameters of CL, V, and V_{max} were 0.223 L/day (SE: 0.62%), 4.62 L (SE: 0.90%) and 5.40 mg/day (SE: 1.0%), respectively, similar to the parameter estimates of the base model (Table 3). A summary of variance and covariance for between-subject-variability is provided in Supplemental Table S2. The precision for all structural model parameters and residual variability estimates was less than 33% SE. Even after accounting for the covariate effects, there was still substantial unexplained BSV on the pharmacokinetic parameters, with estimates of 69.2, 69.6 and 25.9% CV for CL, V, and V_{max} respectively. Total body weight had a large influence on CL (and Q), V (and V_2) and V_{max}, with estimated weight effect exponents of 0.598 (SE: 9.3%), 0.849 (SE: 16%) and 1.12 (SE: 9.0%), respectively. There was relatively high correlation

Table 3. Summary of Brodalumab Parameter Estimates and Covariates Effects for the Final Population PK Covariate Model

Parameters	Model Estimate (%SE)	BSV %CV (%SE)
CL (L/day)	0.223 (0.62%)	69.2% (13%)
V (L)	4.62 (0.90%)	69.6% (19%)
V_{max} (mg/day)	5.40 (1.0%)	25.9% (33%)
K_m (fixed) (μg/mL)	0.02	—
K_a (day^{-1})	0.236 (0.64%)	57.9 (14%)
Q (L/day)	0.697 (13%)	15% (fixed)
V_2 (L)	1.84 (0.61%)	85.6% (17%)
F (fixed) (%)	57.6	—
σ_1 (additive) (μg/mL)	0.384 (8.8%)	—
σ_2 (proportional) (%)	11.9 (3.9%)	

	Parameterization	Model Estimate (95% CI)	Null Value
Covariates affecting CL			
TBW	$TV(TBW/90)^{\theta}$	0.598 (0.49, 0.71)	0
Age	$TV(AGE/40)^{\theta}$	0.468 (0.39, 0.54)	0
Diagnosis	$TV \times \theta^{DIAG}$	0.927 (0.92, 0.94)	1
Covariates affecting Q			
TBW	$TV(TBW/90)^{\theta}$	0.598 (0.49, 0.71)	0
Covariates affecting V and V_2			
TBW	$TV(TBW/90)^{\theta}$	0.849 (0.58, 1.1)	0
Covariates affecting V_{max}			
TBW	$TV(TBW/90)^{\theta}$	1.12 (0.92, 1.4)	0
Age	$TV(AGE/40)^{\theta}$	−0.320 (−0.41, −0.23)	0
Diagnosis	$TV \times \theta^{DIAG}$	1.04 (0.97, 1.1)	1

BSV, between-subject variability; CL, clearance; F, subcutaneous bioavailability; K_a, absorption rate constant; K_m, Michaelis–Menten constant; V, volume of central compartment; V_2, volume of peripheral compartment, V_{max}, maximal transport velocity; Q, intercompartmental transfer clearance; TBW, total body weight; DIAG, diagnosis (0: Healthy Volunteer, 1: Psoriasis Patient); %SE determined by NONMEM covariance step after importance sampling; 95% CI determined by estimate ± 1.96 × SE determined by NONMEM covariance step.

(R = 0.76) between individual random effects for CL and V. Shrinkage for all estimated parameters was less than 26%.

The covariate of TBW and age had the largest influence on CL. The change from the population mean CL for patients with age varying from 18 to 60 years was −31% to 30%, respectively, compared to the 40-year-old, 90 kg psoriatic reference patient. A comparable influence was observed for TBW; changes from the population mean CL for patients with weight varying from 60 to 120 kg was −21% to 19%, respectively. Diagnosis on the other hand only minimally affected CL. Similarly, V_{max} values changed from −36% to 38% for TBW between 60 to 120 kg and from 29% to −16% for ages between 18 and 60 years.

The final covariate model for CL, V, V_{max}, K_a, Q, and V_2 was:

$$TVCL = 0.223\left(\frac{TBW}{90}\right)^{0.598}\left(\frac{AGE}{40}\right)^{0.465}0.927^{DIAG}$$

$$TVV = 4.62\left(\frac{TBW}{90}\right)^{0.849}$$

$$TVV_{max} = 5.40\left(\frac{TBW}{90}\right)^{1.12}\left(\frac{AGE}{40}\right)^{-0.320}1.04^{DIAG}$$

$$TVK_a = 0.236$$

$$TVQ = 0.697\left(\frac{TBW}{90}\right)^{0.598}$$

$$TVV_2 = 1.84\left(\frac{TBW}{90}\right)^{0.849}$$

Simulation

To evaluate the impact of key covariates on the expected area under the concentration–time curve (AUC_{ss}) and maximum serum brodalumab concentrations ($C_{max,ss}$) at steady state, several scenarios were simulated based on the final population PK model. As expected, weight had a pronounced effect on the brodalumab AUC_{ss}. For doses between 140 and 210 mg, the AUC_{ss} was predicted to be greater than ~2-fold higher in subjects weighing less than 75 kg compared to population reference subjects (Figure 3). While diagnosis did not impact the predicted brodalumab exposure, a slight increase in exposure parameters for older individuals and a decrease in $C_{max,ss}$ and AUC_{ss} for younger subjects especially at lower doses was observed (Figure 3).

Discussion

Brodalumab is a human IgG2 monoclonal antibody targeting the IL-17 receptor A (IL-17RA) that has been implicated in the pathogenesis of psoriasis.[4] Binding of brodalumab to IL-17 RA blocks signaling by IL-17A, IL-17F, and IL-17A/F cytokines. Recent clinical trials demonstrated that brodalumab exhibits strong efficacy in treating moderate to severe plaque psoriasis,[12,13] and is currently being evaluated in three Phase 3 studies in psoriasis subjects. In the present manuscript, a population modeling approach using data from phase 1a and phase 2 studies in healthy volunteers and patients with psoriasis and psoriatic arthritis was developed to determine the between-subject variability and estimate the effect of covariates on brodalumab pharmacokinetics (PK).

Brodalumab serum concentration–time profile in healthy adults and patients with psoriasis was described by a two-compartment model with parallel linear and non-linear elimination from the central compartment. The non-linear portion of elimination is especially pronounced at lower doses, which has been described for numerous monoclonal antibodies and is assumed to be due to target binding (target-mediated disposition). Due to finite

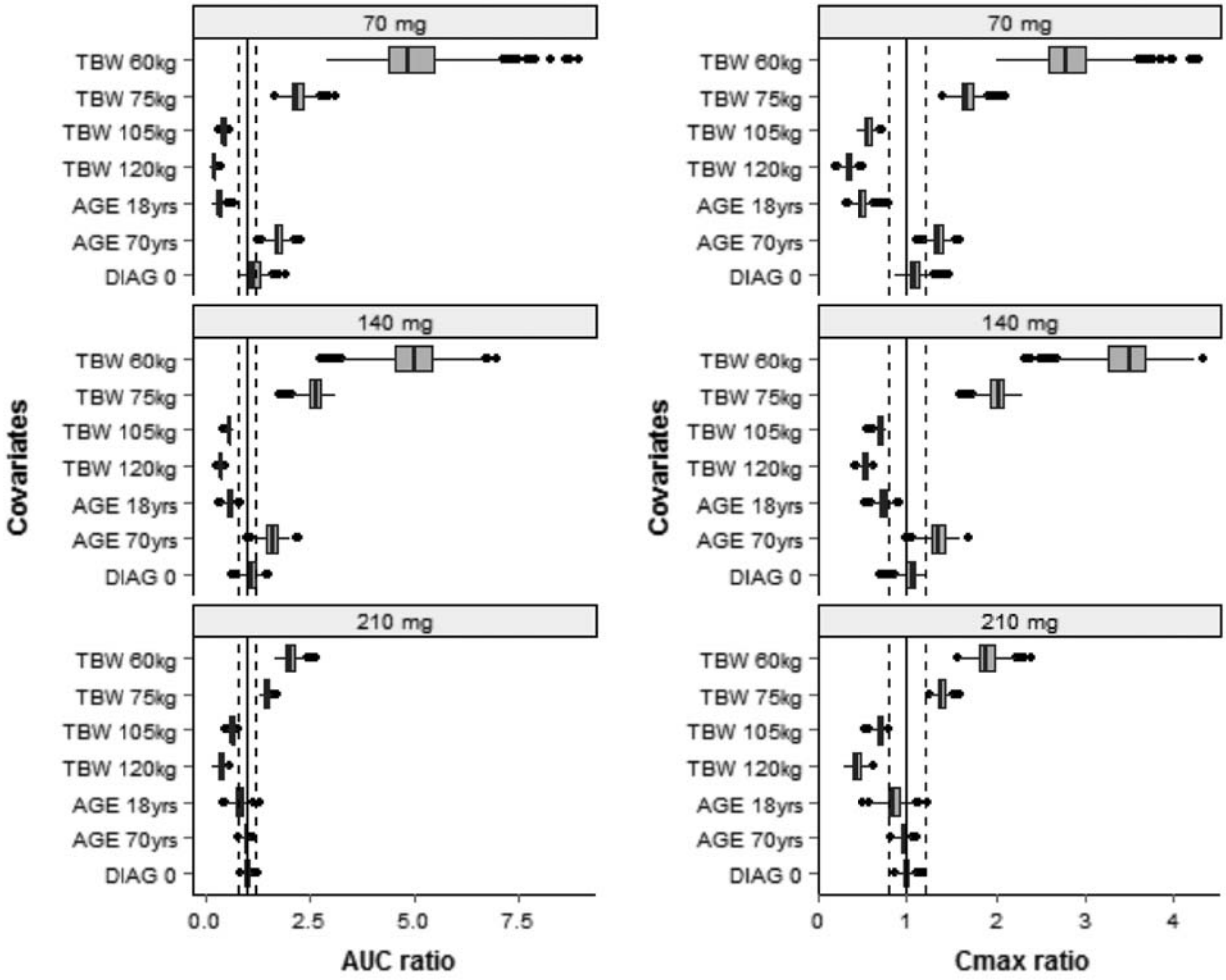

Figure 3. Covariate effects on the area under the curve (AUC_{ss}) and $C_{max,ss}$ for subcutaneous doses of 70, 140, and 210 mg brodalumab. The solid black zero-line represents no covariate effect (psoriatic subject aged 40 years with a total body weight [TBW] of 90 kg) and the dashed lines characterize an effect of ±25%. Boxes represent the 25th–75th percentile, whiskers the 1.5 interquartile range of the uncertainty probability distribution, and symbols depict outliers.

expression of the target, this pathway is saturable; the rate of uptake and elimination is a function of dose and the expression level of the target.[21] The final population estimated PK parameters for brodalumab are comparable to reported values for other antibodies with relatively slow serum clearance of 0.223 L/day (typical CL) as well as low volume of distribution of 4.62 L (typical V), which is indicative of limited tissue penetration and mainly distribution in serum consistent with the large molecular weight of antibodies and their hydrophilicity.[22–24] The between-subject variability was estimated to be 69.2, 69.6 and 25.9% CV for CL, V, and V_{max}, respectively, which is in the range of variability reported for other therapeutic monoclonal antibodies.[24]

In the base and final model, the structural and random variance parameters were estimated with good precision; the goodness-of-fit data and visual predictive check (Figures 1 and 2) provide evidence that the developed structural model was reflective of the observed data and that simulation of individual AUC_{ss} and $C_{max,ss}$ values can be used to model the exposure–response relationship or develop modified dose regimens in varying patient populations.

Analysis of covariates indicated that total body weight and age influence CL, V, and/or V_{max}. The effect of body weight is not surprising since CL and V have often been found to be correlated to body size. Interestingly, only a few reports have identified age as a covariate in population PK analysis of therapeutic monoclonal antibodies. For example, for panitumab, age was negatively correlated with V_{max}, while for efalizumab, age was positively correlated with CL.[25,26] As expected from their effect on the PK parameters CL, V, and V_{max}, age and total body weight are also the main predictors of brodalumab exposure at steady state. For these covariates, the magnitude of change for median AUC_{ss} and $C_{max,ss}$ decreased as the dose increased. This effect can be attributed to parallel linear and non-linear elimination

observed for brodalumab with the non-linear portion having a greater influence on total clearance, and hence AUC_{ss} and $C_{max,ss}$, at lower doses. Based on these simulations, heavier patients would be expected to have decreased exposure and lower $C_{max,ss}$ values then patients with the population mean weight of 90 kg suggesting that dose adjustments might be warranted for SC brodalumab. Similarly, with increasing age increased AUC_{ss} and $C_{max,ss}$ are predicted. The age effect was pronounced at the 70 mg dose of brodalumab; whereas at doses of 140 and 210 mg, the exposure change was less than ~2-fold that of the reference subject. This suggests that the impact of age on exposure is more pronounced for doses where exposure is mainly driven by non-linear processes (ie, lower brodalumab doses). In contrast to age and TBW, diagnosis (healthy vs. psoriasis) as the other investigated covariate fell within the boundary of no clinically significant change with regard to AUC_{ss} and $C_{max,ss}$, suggesting that this parameter is not clinically significant.

In conclusion, serum concentrations of brodalumab were successfully described using a two-compartmental model with parallel linear and non-linear elimination from the central compartment. Patient body weight significantly influenced clearance, volume of distribution, and V_{max}, and had a profound effect on AUC_{ss} and $C_{max,ss}$ Further evaluations based on Phase 3 data are planned to evaluate the impact of body weight and age on the exposure–response of brodalumab.

Declaration of Conflicting Interests

C.J. Endres, D.H. Salinger, K. Köck, D.A. Martin, P. Klekotka, A. Nirula, and M.A. Gibbs are employees and shareholders of Amgen, Inc.

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