

ORIGINAL ARTICLE

Dose Response and Pharmacokinetics of Tofacitinib (CP-690,550), an Oral Janus Kinase Inhibitor, in the Treatment of Chronic Plaque Psoriasis

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Longitudinal nonlinear mixed effects modeling was used to characterize the dose–response profile of tofacitinib using data from a placebo-controlled dose-ranging study, where tofacitinib 2, 5, and 15 mg twice daily (b.i.d.) were evaluated for plaque psoriasis treatment. Bayesian estimation was applied with prior information derived from the literature: nonclinical and clinical data in psoriasis, as well as other indications. The probability to achieve a certain target effect associated with a given dose was calculated from the posterior samples. On the basis of these probabilities along with safety considerations, tofacitinib 5 and 10 mg b.i.d. were selected for further testing in confirmatory phase III clinical trials. Pharmacokinetics in patients with psoriasis was characterized using a population-based modeling approach, and body weight was identified as an important covariate. A subgroup analysis suggested reduced efficacy of tofacitinib with increasing body weight; however, it is unclear whether this trend could be explained by systemic exposure alone.

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Tofacitinib (CP-690,550) is a novel, oral Janus kinase inhibitor that is currently being investigated as a targeted immunomodulator for the treatment of several autoimmune diseases such as psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and dry eye disease, and for prophylaxis of renal transplant rejection.

Tofacitinib has demonstrated efficacy in a 14-day study in patients with psoriasis.¹ An exploratory phase IIb study (A3921047; ClinicalTrials.gov NCT00678210) was designed using a modeling and simulation approach (results on file). The goal was to evaluate the dose response and pharmacokinetics (PK) of tofacitinib in patients with chronic plaque psoriasis together with its correlation with clinical efficacy responses over 12 weeks of treatment.

An E_{\max} (maximum effect) model with Bayesian estimation was used to characterize the dose–response profile. In addition, PK was characterized using a population-based approach. The model-based approaches enabled an understanding of the PK and pharmacodynamic profiles of tofacitinib in patients with chronic plaque psoriasis and allowed the identification of clinically meaningful efficacious dose(s) with acceptable safety profile(s) for further development in confirmatory phase III clinical trials.

RESULTS

Dose–response relationship for PASI75 and PGA

A dose response for proportion of patients with $\geq 75\%$ change from baseline Psoriasis Area and Severity Index (PASI75) and Physician's Global Assessment (PGA) responses over time were observed. The effect of tofacitinib on PASI75 response was evident at week 4; there was a large increase in the response

rate between weeks 4 and 8 with small increases thereafter (Figure 1 and Supplementary Figure S1 online). The PGA response rate paralleled the PASI75 response between weeks 4 and 8 (Figure 2 and Supplementary Figure S2 online). Overall, the observed responder rates were well within the prediction intervals (except 5 mg twice daily (b.i.d.) at week 8 time point), suggesting no obvious misfits to the data.

Posterior distributions of marginal model parameters at week 12 for PASI75 and PGA responses based on the longitudinal model are summarized in Table 1. The posterior distributions of $E_{\max}^m(12)$ (the maximum drug effect) for PASI75 and PGA responses at week 12 are similar, but the posterior distribution of $E_0^m(12)$ (the placebo response) suggests a higher overall placebo response rate for PGA (12%) compared with PASI75 (4%). In addition, the posterior distribution for ED_{50} (dose required to achieve 50% of the maximum effect) suggests a much higher estimate with larger uncertainty for PGA response as compared with PASI75 response.

The results from the dose–response modeling were also used to evaluate the efficacy response over the full range of doses to determine the lowest dose that could achieve a minimum targeted efficacy with high confidence. The specific numerical rule applied was to identify a dose having at least a 50% probability of achieving $\geq 50\%$ response rates for both PASI75 and PGA at week 12. A 50% response rate was considered as the lower end of the desired target effect. Figure 3 shows the probability of the response rates $\geq 50\%$ for PASI75 and PGA at week 12. Doses ranging from 6 to 15 mg b.i.d. of tofacitinib met these criteria. Although the 5 mg b.i.d. dose did not achieve the desired probability for PGA response of at least 50% in response rate (23% vs. a target of $\geq 50\%$)

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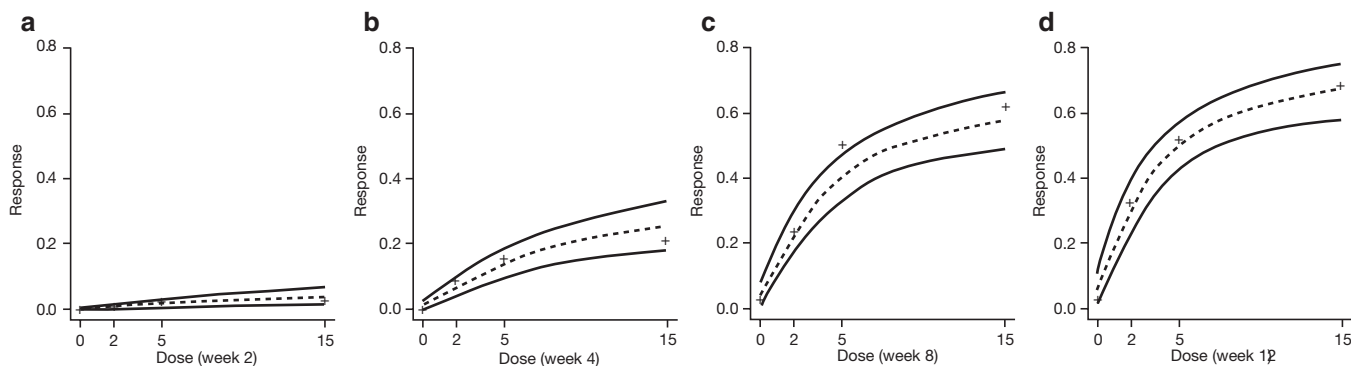


Figure 1 Posterior mean* (80% prediction interval) model-predicted PASI75 response rates at weeks 2, 4, 8, and 12. The dotted line is the posterior mean prediction, bottom and top solid lines represent the 10th and 90th percentiles of the prediction intervals, respectively, and plus symbols represent observed sample proportions. PASI75 response rate, proportion of patients achieving $\geq 75\%$ PASI change from baseline. *Median values are the same as the mean values.

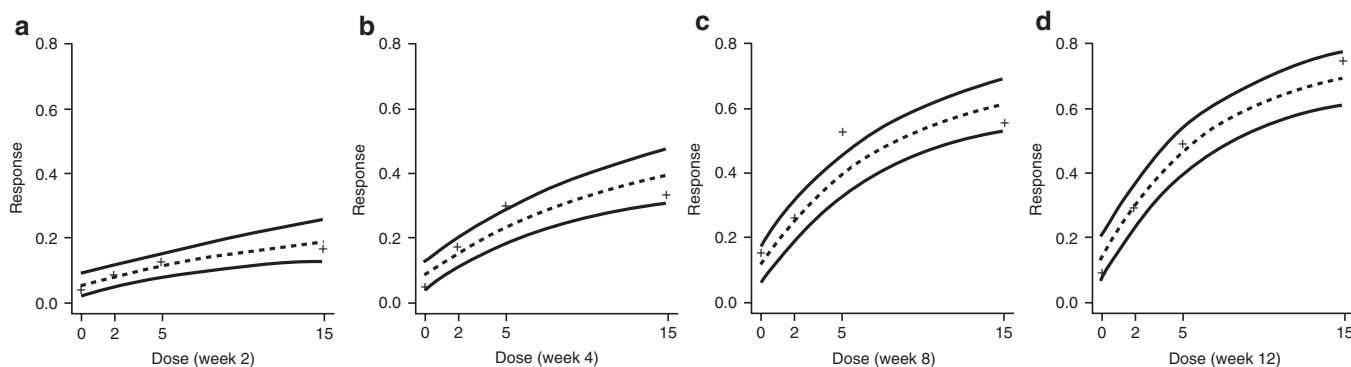


Figure 2 Posterior mean* (80% prediction interval) model-predicted PGA response rates at weeks 2, 4, 8, and 12. The dotted line is the posterior mean prediction, bottom and top solid lines represent the 10th and 90th percentiles of the prediction intervals, respectively, and plus symbols represent observed sample proportions. PGA response rate, proportion of patients assessed as “clear” or “almost clear” on the Physician’s Global Assessment scale. *Median values are the same as the mean values.

(Figure 3), the model predictions for the 5 mg b.i.d. dose suggested an adequate response rate for both PASI75 and PGA (50 and 47%, respectively) (Table 1). Hence, the 5 mg b.i.d. dose was considered as the lowest dose that can be carried forward for further development in phase III to achieve efficacy associated with desired target effect. The 10 mg b.i.d. dose was also determined to warrant further development as it was estimated to provide at least 10% additional efficacy over 5 mg b.i.d. at week 12 (Table 1). This is also reflected in the higher probability of achieving the desired efficacy for 10 mg b.i.d. as compared with 5 mg b.i.d. for both PASI75 (99 vs. 49%) and PGA responses (99 vs. 23%) (Figure 3).

Similarly, a probabilistic decision criteria for a safety laboratory end point (hemoglobin change) was applied to facilitate phase III dose selection.² Doses with $>50\%$ probability of showing a placebo-adjusted incidence of $<5\%$ for >2 g/dl drop in hemoglobin were considered for phase III evaluation. Tofacitinib 5 and 10 mg b.i.d. were selected as they met this criterion (100 and 87%, respectively).

Dose–response relationship for PASI75 with alternative priors and modeling with time-varying ED_{50}

To assess the sensitivity of the dose–response profile due to the specification of the priors, the posteriors were recomputed under the alternative priors for PASI75 responses, and the

resulted dose selection based on the probability to achieve the targeted effect for PASI75 were evaluated. The impact of prior distribution of ED_{50} and $E_{max}(12)$ was assessed as they were the most informative. The prior distribution for ED_{50} was specified as uniform distribution on the interval of (0, 30) (as opposed to skewed beta distribution scaled to the same range) and the prior distribution for $E_{max}(12)$ was still to have normal distribution, but with mean 0 (as opposed to mean 1.5) on the probit scale.

The posterior median for ED_{50} was 2.68 mg and the 10th and 90th percentiles were 1.28 and 6.27 mg (which is a little more skewed toward right as compared with the beta distribution; see Table 1 for PASI75 response). For $E_{max}(12)$, the posterior median was 2.58 and the 10th and 90th percentiles were 2.10 and 3.11, which were almost identical to the values in Table 1 for PASI75 response. Therefore, for the two parameters, the difference in posterior distribution between the original priors and the alternative priors were not large enough to impact the dose selection.

In addition, a time-varying “apparent” $ED_{50}(W)$ parameter was also considered, in which $ED_{50}(W)$ was parameterized as a decreasing function of time (ED_{50} divided by $(1 - \exp(-K_{50}W))$). With a uniform prior for $(1 - \exp(-K_{50}W))$ at week 2, specified as uniform distribution on the interval (0.05, 1). The 10th, 50th, and 90th percentiles for ED_{50} at week 12

Table 1 Posterior distributions of parameters and proportions of PASI75 response and PGA response at week 12

	PASI75 response				PGA response			
	Mean (SD)	10%	50%	90%	Mean (SD)	10%	50%	90%
Model parameters								
E_0^m (0)	-4.33 (0.59)	-5.11	-4.31	-3.58	-2.0 (0.32)	-2.42	-1.97	-1.63
P_0^m	2.60 (0.62)	1.78	2.62	3.41	0.86 (0.37)	0.40	0.84	1.34
Ps0	0.31 (0.07)	0.22	0.30	0.40	0.28 (0.10)	0.18	0.26	0.42
E_0^m (12)	-1.82 (0.36)	-2.29	-1.80	-1.37	-1.18 (0.20)	-1.45	-1.17	-0.93
ED_{50}^m mg	2.59 (1.77)	1.09	2.12	4.56	7.37 (4.87)	2.74	5.98	14.06
E_{max}^m (12)	2.68 (0.41)	2.17	2.66	3.22	2.56 (0.60)	1.90	2.48	3.35
K_{max}	0.41 (0.17)	0.25	0.38	0.61	0.25 (0.13)	0.12	0.23	0.39
Estimated proportions								
Placebo b.i.d.	0.04 (0.03)	0.01	0.04	0.09	0.12 (0.04)	0.07	0.12	0.19
Tofacitinib 2 mg b.i.d.	0.30 (0.05)	0.22	0.29	0.38	0.29 (0.04)	0.23	0.29	0.36
Tofacitinib 5 mg b.i.d.	0.50 (0.05)	0.43	0.51	0.58	0.47 (0.05)	0.40	0.47	0.54
Tofacitinib 10 mg b.i.d. ^a	0.63 (0.05)	0.56	0.63	0.70	0.63 (0.05)	0.55	0.63	0.70
Tofacitinib 15 mg b.i.d.	0.68 (0.06)	0.60	0.68	0.76	0.70 (0.06)	0.62	0.70	0.78
$E_0(12) + E_{max}(12)^b$	0.79 (0.08)	0.68	0.79	0.90	0.88 (0.09)	0.75	0.89	0.99

^aTofacitinib 10 mg b.i.d. was an untested dose in this study; ^b $(E_0(12) + E_{max}(12))$ represents the model projected maximum response in proportion at week 12. b.i.d., twice daily; E_0 , effect for placebo; ED_{50} , a dose that achieves 50% of the maximum effect; E_{max} , maximum effect; PASI75, proportion of patients with $\geq 75\%$ change from baseline PASI (Psoriasis Area and Severity Index); PGA, Physician's Global Assessment; PGA response, proportion of patients assessed "clear" or "almost clear" at week 12.

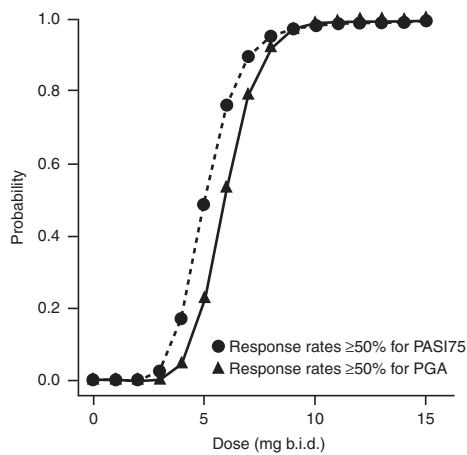


Figure 3 Probability of achieving the target efficacy effect at week 12 of at least 50% response rate for PASI75 or Physician's Global Assessment (PGA) response by dose. PASI75 response rate, proportion of patients achieving $\geq 75\%$ Psoriasis Area and Severity Index (PASI) change from baseline. PGA response rate, proportion of patients assessed as "clear" or "almost clear" on the scale; b.i.d., twice daily.

were 1.12, 2.19, and 4.28 mg, respectively, which are very close to the time-independent estimate of ED_{50} (see **Table 1** for PASI75 response).

Population PK analysis

A one-compartment model with first-order absorption was used to characterize the PK of tofacitinib in patients with

psoriasis (**Supplementary Figure S3** online). Parameter estimates from the base and final model are summarized in **Table 2**. Apparent oral clearance (CL/F) and apparent volume of distribution (V/F), where F is the bioavailable fraction, were estimated to be 25 l/h and 109 l with 39 and 50% IIV (inter-individual variability), respectively. The interoccasion variability on the scaling parameter F was estimated to be 33%. Among the tested covariates, only body weight on V/F was found to be significant ($P < 0.001$). Over the observed weight range of 42 to 186 kg, weight was found to be a covariate of V/F but not CL/F. Modeling suggested that V/F increased with body weight (the estimated exponent for the weight effect on V/F was 0.59). The steady-state systemic exposures were found to be proportional to dose.

Relationship among body weight, efficacy, and PK

The efficacy data were explored by stratifying into quartiles of body weight (≤ 72.6 kg, >72.6 to ≤ 90 kg, >90 to ≤ 101 kg, and >101 kg). Although the sample size in these quartiles was small (**Supplementary Table S1** online), there appeared to be a trend toward lower response rates in heavier patients, with PGA response exhibiting an overall higher responder rate for the lowest weight quartile and PASI75 displaying a similar trend for the tofacitinib 5- and 15-mg groups (**Figure 4**). For tofacitinib 15 mg b.i.d., the difference between the lowest and highest weight quartiles was 22% (75 vs. 53%) for PASI75 and 25% (92 vs. 67%) for PGA response rates.

However, since exposure did not parallel the efficacy-weight relationship, it is unclear whether the possible trend toward lower PASI75 and PGA responses with higher body

weight could be explained by systemic exposure. When the model-predicted exposure measures were evaluated based on the aforementioned quartiles across the three doses (Supplementary Table S2 online), mean C_{max} (maximum plasma concentration) and C_{min} (minimum plasma concentration) were ~13% lower and 41% higher, respectively, in the highest weight quartile as compared with the lowest weight quartile, whereas the model-predicted average concentration (C_{avg}) was similar between these groups (ratio: 0.99). The lower C_{max} and the higher C_{min} in heavier patients was consistent with the covariate analysis showing body weight as influencing V/F but not CL/F.

The small decline in C_{max} with weight did not appear to account for the larger magnitude of change in the efficacy

measures with weight. C_{avg} did not change appreciably and C_{min} demonstrated an opposite trend.

DISCUSSION

The study reported here exemplifies the benefits of a modeling approach in drug development to aid clinical decision making. Modeling-based methodology is frequently used to optimize clinical study design and to understand the dose–response relationship. For example, modeling allows efficacy across doses to be shown without the need for costly additional clinical trials, allows exploration of relationships between patient characteristics and PK parameters, and enables assessment of exposure and response in the target population.^{3–5} The longitudinal E_{max} dose–response model adequately characterized the dose–response profile of tofacitinib for both PASI75 and PGA responses at each time point (week 2, 4, 8, and 12). Data from the previously conducted 14-day study¹ in healthy subjects with psoriasis were not pooled with the data from this phase IIb study because the efficacy end points were different in the two studies. However, the information from the 14-day study was used to help construct the prior distributions for some of the model parameters.

An advantage of longitudinal dose–response modeling is that it uses the totality of data and the doses are modeled as a continuous variable. This enables inferences to be drawn for any dose (from a range of active doses) across all time points as opposed to a pairwise comparison procedure, in which the inference can only be drawn for the tested dose at a single time point. Furthermore, the Bayesian approach allows an integration of prior knowledge generated from nonclinical and preclinical, as well as clinical experiments, in an explicit way through the specification of priors for efficacy. This differs from the conventional frequentist approach of drawing inferences solely from the conducted experiment. In this application, the Bayesian estimates would be expected to yield comparable

Table 2 Parameter estimates for the base and final population PK models

Parameter	Base	Final
	Estimate (RSE, %)	Estimate (RSE, %)
OFV	841.96	817.49
Ka (h ⁻¹)	1.3 (11.3)	1.27 (11.1)
CL/F (l/h)	24.8 (5.2)	24.7 (5.1)
V/F (l)	126 (8.1)	109 (8.1)
ϵ_1^a	71.8 (7.6)	71.8 (7.6)
ϵ_2^a	219 (36.5)	227 (40.0)
BWT on V/F	–	0.586 (23.0)
IIV ^b CL	0.154 (20.6)	0.156 (20.2)
IIV ^b V	0.273 (25.3)	0.248 (25.4)
IOV ^b F	0.118 (33.1)	0.111 (34.7)

RSE was reported by NONMEM.

^aResidual SD reported as the approximate percent coefficient of variation (%CV); ^bIIV values as the approximate %CV (%CV = $\sqrt{\omega^2} \times 100$), for the base and final model are: CL/F (l/h) 39 and 39%, respectively; V/F (l) 52 and 50%, respectively; ^cIOV value as the approximate %CV (%CV = $\sqrt{\omega^2} \times 100$), for the base and final model for F is 34 and 33%, respectively).

BWT, baseline body weight; CL/F, apparent oral clearance; ϵ , residual SD; F, bioavailable fraction; IIV, interindividual variability; IOV, interoccasion variability; Ka, absorption rate constant; OFV, objective function value; PK, pharmacokinetics; RSE, residual SE; V/F, apparent volume of distribution.

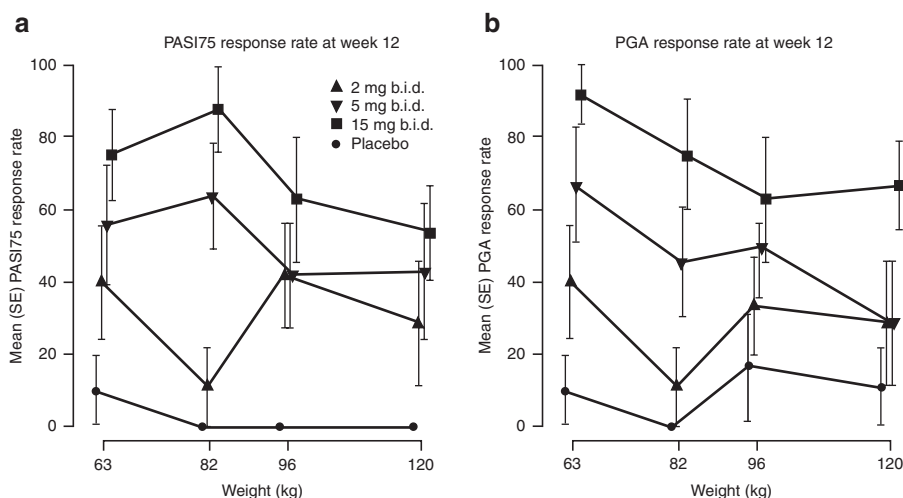


Figure 4 PASI75 response rate and PGA response rate as a function of weight for the different treatment groups. PGA response rate, proportion of patients assessed as “clear” or “almost clear” on the Physician’s Global Assessment (PGA); PASI75 response rate, proportion of patients achieving $\geq 75\%$ PASI (Psoriasis Area and Severity Index) change from baseline. Mean values of the observed response rates (PGA response and PASI75 response) are presented with ± 1 SE (error bars). Body weights were binned based on weight quartiles (≤ 72.6 kg, >72.6 to ≤ 90 kg, >90 to ≤ 101 kg, and >101 kg); median weights within these quartiles are shown. b.i.d., twice daily.

estimates as maximum likelihood estimation due to the weakly informative priors.

An obvious advantage of Bayesian estimation is that inferences for PASI75 and PGA response can be drawn based on the posterior distribution which provides a probabilistic assessment for these clinical end points. This probabilistic assessment enabled us to identify an optimal dose range for phase III evaluation. Dose selection for phase III was based on the probability to achieve a clinically meaningful target effect. This probability was derived using knowledge of dose/exposure–response relationships by considering the clinical relevance of the target effect and the desired confidence in the effect size. This methodology provided a quantitative and objective framework to rank the performance of doses for decision making. Bayesian estimation demonstrated tofacitinib 5 mg b.i.d. dose as the minimum effective dose in treating patients with chronic plaque psoriasis with high confidence. In addition, 10 mg b.i.d. was predicted to offer an increased benefit in efficacy while also meeting the criteria for a laboratory end point change (hemoglobin).

Population analysis of tofacitinib plasma concentrations revealed dose-proportional PK in this patient population. Baseline weight, age, creatinine clearance, sex, race, and PASI score were tested as covariates on CL/F and V/F. Only body weight was found to significantly impact V/F, but not CL/F.

An examination of the week 12 PASI 75 and PGA response measures suggested a decrease in efficacy with increasing weight, a trend also noted for other psoriasis systemic and biologic treatments. A review of the effect of body weight on the efficacy of various fixed-dose biologic treatments suggested that the optimal responses were less frequent in patients with increasing body weight.⁶ In the case of tofacitinib, steady-state systemic exposures (C_{\max} , C_{avg} , and C_{\min}) did not show any appreciable or consistent difference with respect to weight. However, this needs to be confirmed in phase III trials where a larger sample size, and PK sampling will enable a more robust characterization of covariate relationships, especially relating to any potential effects of weight on the PK. Nevertheless, data from this study suggest that PK may not entirely explain the observed difference in efficacy with body weight.

The potential efficacy–weight relationship reported in this study is of clinical interest in light of current thinking that white adipose tissue is an active secretory organ involved in the regulation of several physiological and pathological processes, including immunity and inflammation. Adipocytes and other associated adipose tissue cells produce a number of inflammatory cytokines and chemokines.^{7–9} Production of these can be pathologically dysregulated in disease states, and obesity itself is characterized by low-grade chronic systemic inflammation; this is evidenced by elevated inflammatory markers, such as C-reactive protein and interleukin-6.^{7,8} However, it is currently unclear why homeostatic mechanisms that normally prevent overactive immune responses fail in cases of obesity.⁸ The observed difference in outcome according to patients' weight in the study reported here adds further evidence for the proinflammatory properties of adipose tissue.

In conclusion, the study was designed to adequately characterize the dose–response relationship of tofacitinib in patients with moderate-to-severe chronic plaque psoriasis. Inferences drawn from Bayesian modeling were applicable to a range of doses and not limited to the tested doses only. The data modeling helped to select 5 and 10 mg b.i.d. tofacitinib for further development in confirmatory phase III clinical trials, even though 10 mg b.i.d. dose was not a tested dose in this study.

METHODS

Patients

In this randomized, double-blind, parallel-group, placebo-controlled, multicenter study, tofacitinib was investigated for the treatment of patients with moderate-to-severe chronic plaque psoriasis. A total of 197 patients with moderate-to-severe chronic plaque psoriasis were randomized to tofacitinib 2 mg b.i.d. ($n = 49$), 5 mg b.i.d. ($n = 49$), 15 mg b.i.d. ($n = 49$), or placebo ($n = 50$) for 12-week treatment and had visits at baseline, weeks 2, 4, 8, 12, 14, and 16. Discontinuations while on treatment occurred in placebo ($n = 14$, 28%), 2 mg b.i.d. ($n = 5$, 10.2%), 5 mg b.i.d. ($n = 9$, 18.4%), and 15 mg b.i.d. ($n = 5$, 10.2%). The primary end point was the proportion of patients achieving $\geq 75\%$ reduction in PASI (PASI75) after 12 weeks of treatment, and the key secondary end point was the PGA response, i.e., the proportion of patients assessed “clear” or “almost clear” at week 12. Full details of the trial design, eligibility, exclusion criteria, and patient population have been described elsewhere.¹⁰

The study was performed in compliance with the International Conference on Harmonization Good Clinical Practice Guidelines; all patients provided written informed consent, and institutional review boards or ethics committees approved the protocol before the study started.

Bayesian longitudinal dose–response model

Model specification. PASI75 and PGA responses were binary end points, with value 1 indicating a responder while value 0 indicated a nonresponder. A longitudinal E_{\max} model with time-variant was used to characterize the dose–response relationship of tofacitinib on PASI75 and PGA responses over time. This model is an extension of the univariate E_{\max} model derived from drug receptor–binding models,¹¹ and a similar model has been used to characterize the dose–response profile in rheumatoid arthritis patients treated with tofacitinib.¹²

The model states that the probability of a patient achieving PASI75 or PGA response can be modeled as shown below:

$$\Pr(Y = 1|D, W, \delta) = \Phi\left(E'_0(W) + \frac{E'_{\max}(W)D}{ED_{50} + D} + \delta\right),$$

where Y is the binary end points of PASI75 or PGA response, D refers to dose, W refers to week, and δ is a random patient-specific term normally distributed with mean 0 and SD σ . Φ is the cumulative distribution function of the standard normal distribution, and “ l ” superscripts represent the time-varying functions.

The term $E_0^l(W)$ is a function of time representing the placebo response rate over time: $E_0^l(W) = E_0 + P_0(1 - e^{-P_{s0}W})$ depending on the parameters E_0 , P_0 , and P_{s0} . E_0 is the placebo response at baseline, P_0 is the maximum change over time in placebo response, and $1 - e^{-P_{s0}W}$ is the proportion of the maximum placebo response achieved at week W .

The parameter ED_{50} is the dose achieving 50% of the maximum effects (on the probit scale). It represents the potency of the compound and is fixed over time. The term $E_{max}^l(W)$ represents the E_{max} as a function of time $E_{max}^l(W) = E_{max}(1 - e^{-K_{max}W})$ depending on the parameters E_{max} and K_{max} .

The equation evaluated at week 12, which is in the form of a univariate E_{max} model, gives the following equation:

$$\Pr(Y = 1|D, W = 12) = \Phi\left(E_0^m(12) + \frac{E_{max}^m(12)D}{ED_{50} + D}\right),$$

where $E_0^m(12) = (1 + \sigma^2)^{-1/2} E_0^l(12)$ and $E_{max}^m(12) = (1 + \sigma^2)^{-1/2} E_{max}^l(12)$, which were used to help to specify the prior distributions.

Prior distributions. The prior distributions for the parameters in $E_0^l(W)$, ED_{50} , and $E_{max}^l(W)$ were derived based on the prior distribution for the marginal probit parameters $E_0^l(12)$, ED_{50} , and $E_{max}^m(12)$ conditioning on σ .

$$E_0^m(12) \sim N(-1.65, SD = 2), ED_{50}(12) \sim 30 \text{ Beta}(0.38, 1.5), E_{max}^m(12) \sim N(1.5, SD = 2)$$

A review of historical trials with other psoriasis systemic therapies suggested PASI75 or PGA response rates for placebo were ~5% after 8–12 weeks, but with a right-skewed distribution on the proportion scale due to an occasional high placebo response rate.^{13–18} The prior for $E_0^m(12)$ was specified to be a normal distribution with mean -1.65 , corresponding to 5% on the proportional scale, and SD 2. An increase of 2 from the mean on the probit scale corresponds to a 65% probability to achieve a PASI75 or PGA response. This increase exceeds any historical placebo PASI75 or PGA responses from literatures, so a prior SD = 2 will be used to represent weak prior information on the probit scale.

The prior for $E_{max}^m(12)$ was specified to be a normal distribution with mean 0 on the probit scale. The prior information for $E_{max}^m(12)$ was chosen based on the preclinical data and clinical evidence of activities in psoriasis,¹ as well as the evidence from the related disease areas for tofacitinib.^{19,20}

Projections of ED_{50} from mice and rat models ranged from 1.5 mg to ~10 mg tofacitinib b.i.d. (depending on species and end point). The estimated ED_{50} from rheumatoid arthritis clinical trials²¹ suggested that ED_{50} for tofacitinib in rheumatoid arthritis disease was around 3 mg. Moderate activity was also observed in a 14-day study¹ of patients with psoriasis at the 10 mg b.i.d. dose, and doses between 20 and 50 mg b.i.d. displayed high (approximately equal) efficacy, indicating an ED_{50} from this very short study for the psoriasis indication below the 20 mg b.i.d. dose. The ED_{50} was assigned a skewed beta prior distribution with parameters (0.38, 1.5) scaled to the range of

0–30 mg b.i.d., which is twice that of the highest dose in the study. The parameter P_0 represents the maximum change at different times in placebo. Data from numerous historical trials showed consistently increasing placebo response, so the prior distribution is restricted to positive values and specified as following:

$$(1 + \delta^2)^{-1/2} P_0 \sim 4 \text{ Beta}(1, 2).$$

There are 0.13, 0.29, and 0.50 prior probabilities that the approximate maximum increase on the probit scale is <1, 2, and 3, respectively.

For the time trend parameter P_{s0} for placebo response, the prior distribution is:

$$1 - e^{-P_{s0}12} \sim 0.8 + 0.2 \text{ Beta}(2, 1)$$

This prior distribution implies probabilities 0.75, 0.44, and 0.10 that 90, 95, and 99% of the placebo response is reached at week 12.

On the basis of the experience with other anti-inflammatory drugs in psoriasis and clinical experience with the current drug in a different indication, some of the drug effect will be achieved by week 2. The prior distribution for proportion of the parameters at equilibrium achieved at week 2 is a uniform distribution:

$$1 - e^{-K_{max}2} \sim U(0.05, 1),$$

which implies high uncertainty about the proportion of the response achieved by week 12. The prior distribution was bounded away from zero to exclude unreasonably large and numerically unstable values.

The prior for patient-specific variability δ is scaled to interval 1–4 from a Beta distribution with the two shape parameters both to be 1.1. This is a nearly flat distribution over a range very likely to include this parameter. Historical trials showed that PASI75 response and PGA response had similar time trend and magnitude^{13–18,22,23} and that prior distributions were weakly informative. As such, the same priors were used for both PASI75 response and PGA response.

Parameter estimation. All the observed cases up to week 12 were used. The missing values were assumed to be missing at random and implicitly handled by longitudinal mixed model. Bayesian estimation was implemented in WinBUGS v1.4.3 to characterize the dose–response profile.²⁴ Inference was based on Markov Chain Monte Carlo methodology; total of 30,000 samples from 3 chains after the initial burn-in of 30,000 samples for each chain. The convergence of the parameter estimates was monitored by Gelman–Rubin statistics.²⁵

Two residual error parameters were used in the model. The rationale for the two residual error parameters was the presence of trough (predose) samples at some visits that appeared to reflect peak concentrations (~4%), possibly due to some patients inadvertently administering a dose before their in-clinic visit. The log-normal residual error model was used.

Population PK model

PK data were available from 131 nonplacebo patients contributing 1,030 measurable tofacitinib concentration samples. Blood samples for PK analysis were collected at week 4 (predose: -2 h; predose and postdose: 0.5 h), week 8 (predose, postdose: 1 and 2 h, respectively), and week 12 (predose: -1 h; predose and postdose: 1 h).

The “base-full-final” model approach was used for model development to characterize PK in patients with psoriasis and explore the impact of covariates on PK. The model was fit using the first-order conditional approximation to the likelihood in NONMEM.

The PK of tofacitinib were best described using a one-compartment model with first-order absorption. The disposition kinetics were modeled using a parameterization involving CL/F and V/F, where F is the bioavailable fraction. A first-order absorption rate constant (k_a) was used to characterize the absorption process. The closed form solution for this model is given by the following equation:

$$C_p = \frac{F \cdot \text{DOSE} \cdot k_a}{V \cdot (k_e - k_a)} (e^{-k_a \cdot t} - e^{-k_e \cdot t}),$$

where C_p is the systemic plasma concentration; k_e is the elimination rate constant defined as the ratio CL/V.

Interindividual and interoccasion variability in the PK parameters were modeled as multiplicative exponential random effects. Residual variability was modeled using a log-transformed error model.

Once the base model was developed, covariates of clinical interest were included in the model to quantify their impact on CL/F and V/F. Covariates were included if their addition resulted in a significant reduction in the OFV (a decrease of at least 3.84; $\alpha = 0.05$, 1 degree of freedom). Backward elimination was used to remove covariates from the full model to arrive at the final model (ΔOFV : 10.83; $\alpha = 0.001$, 1 degree of freedom). The covariates that were tested included baseline weight, age, estimated creatinine clearance (Cockcroft–Gault), sex, race, and baseline PASI score. The final model was intended to provide the most parsimonious description of the data by incorporating the effect of covariates to explain the variability in structural model parameters. Population PK model was evaluated using diagnostic plots such as concordance plots, weighted residual error plots, weighted residual error distribution plots and random effects distribution plots, and simulation-based diagnostics such as posterior predictive check.

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Conflict of Interest. H.T., P.G., and S.K. are employees of Pfizer. J.H. (formerly of Pfizer, USA) is an employee of Novartis Pharma AG, Switzerland. S.C. is an employee of Ann Arbor Pharmacometrics Group, Ann Arbor, MI, USA. K.A.P. is an employee of Probit Medical Research, Canada, and has associations with the following companies: Abbott, Amgen, Astellas, Celgene, Centocor, Eli Lilly, Janssen, Johnson and

Johnson, Galderma, Genentech, Graceway, GlaxoSmithKline, Merck, Novartis, Pfizer, Stiefel, UCB. A.M. is an employee of the Baylor Research Institute, TX, USA, and has associations with the following companies: Abbott, Allergan, Amgen, Astellas, Asubio, Celgene, Centocor, DUSA, Eli Lilly, Galderma, Genentech, Novartis, Novo Nordisk, Pfizer, Promius, Stiefel, Syntrix Biosystems, Warner Chilcott, and Wyeth. B.S. is an employee of University of Connecticut School of Medicine, Farmington, CT, USA, and has associations with the following companies: Abbott, Amgen, Centocor/Johnson and Johnson, Galderma, Leo Pharma, and Stiefel. R.G.L. is an employee of the Dalhousie University, Halifax, Canada, and has associations with the following companies: Abbott, Amgen, Centocor/Ortho Biotech, Pfizer, Novartis, and Celgene.

Author Contributions. All authors have full access to all the study data. H.T., P.G., J.H., R.W., S.C., A.M., B.S., R.G.L., S.K., and K.A.P. wrote the manuscript, designed the research, performed the research, and H.T., P.G., S.C., and S.K. analyzed the data.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

- ✓ Modeling-based methodology is increasingly used to optimize drug development, but published examples demonstrating its application in progressing optimal doses for phase III evaluation are rare.

WHAT QUESTION THIS STUDY ADDRESSED?

- ✓ We investigated the use of modeling-based methodology to predict the performance of tofacitinib doses (range: 1–15 mg b.i.d.) for the treatment of chronic plaque psoriasis, to enable optimal phase III study design.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

- ✓ The modeling exercise enabled inferences to be made on a range of tofacitinib doses, not limited to the tested doses only. Modeling helped select tofacitinib 5 and 10 mg b.i.d. for phase III development. The efficacy of tofacitinib (PASI75 and PGA responses) showed a decline with increasing patient body weight. However, this decline could not be attributed to change in exposure alone, thereby raising the possibility of an intrinsic pharmacodynamic interaction with respect to weight.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

- ✓ Modeling exercises can optimize clinical trial design. Optimum tofacitinib dosing may require consideration of patient body weight.

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