Model-Informed Development and Registration of a Once-Daily Regimen of Extended-Release Tofacitinib

M Lamba[1], MM Hutmacher[2], DE Furst[3], A Dikranian[4], ME Dowty[5], D Conrado[1], T Stock[6], C Nduaka[6], J Cook[1] and S Krishnaswami[1]

Extended-release (XR) formulations enable less frequent dosing vs. conventional (e.g., immediate release (IR)) formulations. Regulatory registration of such formulations typically requires pharmacokinetic (PK) and clinical efficacy data. Here we illustrate a model-informed, exposure–response (E-R) approach to translate controlled trial data from one formulation to another without a phase III trial, using a tofacitinib case study. Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). E-R analyses were conducted using validated clinical endpoints from phase II dose–response and nonclinical dose fractionation studies of the IR formulation. Consistent with the delay in clinical response dynamics relative to PK, average concentration was established as the relevant PK parameter for tofacitinib efficacy and supported pharmacodynamic similarity. These evaluations, alongside demonstrated equivalence in total systemic exposure between IR and XR formulations, provided the basis for the regulatory approval of tofacitinib XR once daily by the US Food and Drug Administration.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Registration of alternative formulations, doses, and regimens to approved drugs has typically required confirmatory clinical efficacy trials, despite regulatory guidance describing the potential for well-understood E-R relationships as the basis for translating efficacy and safety.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The study addressed the question of which PK parameter was most relevant for tofacitinib efficacy and whether the body of evidence from E-R analyses supported the conclusion of similar efficacy between IR and XR formulations.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ The multidimensional analyses demonstrated that average concentration over the dosing interval is the relevant PK parameter for tofacitinib efficacy. E-R analyses and PK studies provided the evidence to conclude that efficacy of tofacitinib XR will be similar to that of tofacitinib IR, thereby serving as the basis for registration without a phase III study.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

☑ Robust dose–response studies and E-R relationships can facilitate efficient drug development and registration strategies, including providing sufficient evidence without the need for confirmatory clinical trials.

Extended-release (XR) formulations release the active ingredient at an intentionally modified rate relative to the conventional/immediate-release (IR) formulations in order to achieve treatment goals, which may include improved convenience and compliance through less frequent dosing and/or improved benefit:risk through modifications to the pharmacokinetic (PK) profile. A robust understanding of the PK and pharmacodynamic (PD) attributes of a drug via model-based approaches provides the cornerstone to the development of these alternative dosage forms.[1] A well-defined exposure–response (E-R) relationship can enable translation of efficacy and safety from one formulation to another, as has been described in the 1998 United States (US) Food and Drug Administration (FDA) guidance on clinical effectiveness.[2] However, we are not aware of a previous application of model-informed bridging between alternate regimens and formulations without a phase III trial of the new formulation in the relevant patient population. The purpose of the current investigation was to illustrate this application using a case study of tofacitinib, where E-R relationships served as the basis for translating controlled trial data from the original IR formulation to the XR formulation to support the registration of an XR dosage form.

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). This chronic autoimmune disease is characterized by synovial inflammation and hyperplasia,

[1]Pfizer Inc, Groton, Connecticut, USA; [2]Ann Arbor Pharmacometrics Group, Ann Arbor, Michigan, USA; [3]University of California, Los Angeles, California, USA; [4]San Diego Arthritis Medical Clinic, San Diego, California, USA; [5]Pfizer Inc, Cambridge, Massachusetts, USA; [6]Pfizer Inc, Collegeville, Pennsylvania, USA. Correspondence: S Krishnaswami (sriram.krishnaswami@pfizer.com).

Received 13 July 2016; accepted 9 November 2016; advance online publication 9 February 2017. doi:10.1002/cpt.576

autoantibody production, and cartilage and bone destruction.[3] The clinical effectiveness of tofacitinib in RA was demonstrated in several phase II,[4–8] phase III,[9–14] and long-term extension[15] trials. Tofacitinib IR was first approved in the US in 2012 at a dose of 5 mg twice daily (b.i.d.).

For chronic conditions in some patients, a once-daily (q.d.) dosing option offers a greater degree of compliance compared to more frequent dosing regimens.[16,17] To enable q.d. dosing with tofacitinib, an XR formulation based on extrudable core system technology was developed at a dose of 11 mg.[18] A series of biopharmaceutical studies in healthy volunteers characterized the PK properties. Results from these studies demonstrated equivalence, using the standard bioequivalence (80–125%) criteria, in both area under the plasma concentration–time curve (AUC) and maximum plasma concentration (C_{max}) of XR 11 mg q.d. compared to IR 5 mg b.i.d. At steady state, minimum plasma concentration (C_{min}) for the XR formulation was 29% lower than the IR formulation.[18]

The primary objective of the current investigation was to determine whether a similar level of efficacy between XR 11 mg q.d. and IR 5 mg b.i.d. could be concluded on the basis of E-R evaluations of nonclinical and clinical data from randomized controlled trials of the IR formulation. Specifically, our objectives were to characterize the PK parameter (AUC or C_{max} or C_{min}) that was most relevant for efficacy and evaluate the clinical relevance of differences in C_{min} between the two formulations.

RESULTS

A set of complementary E-R analyses was performed, which consisted of: 1) identification of the PK parameter most predictive of tofacitinib efficacy in a nonclinical model of inflammation; 2) characterization of delay in the dynamics of clinical response and PK time-course; 3) evaluation of the impact of C_{min} differences on clinical efficacy when the IR formulation was administered in q.d. and b.i.d. regimens; and 4) determination of the PK parameter that best described clinical efficacy.

Modeling nonclinical efficacy data

The relationship between efficacy and dosing regimen was evaluated in a murine collagen-induced arthritis (mCIA) model, wherein vehicle and a range of fixed total daily doses of tofacitinib were administered either q.d. or b.i.d.[19] **Figure 1** shows the relationship from a maximum effect (E_{max}) model between fractional area under the severity time course and drug-exposure predictors. For each PK parameter, the respective concentration that produced 50% of the maximal efficacy (i.e., maximum concentration producing 50% of the maximal effect (EC_{max50}), average concentration producing 50% of the maximal effect (EC_{av50}), minimum concentration producing 50% of the maximal effect (EC_{min50})) was determined.

Good alignment of the q.d. and b.i.d. E-R curves was observed when average drug concentration in the dosing interval (C_{av}, which offers the same interpretation as AUC since C_{av} is proportionally related to AUC as AUC/dosing interval) was used as the predictor of response. In contrast, significant divergence was observed when C_{max} or C_{min} was used as the predictor. Supporting

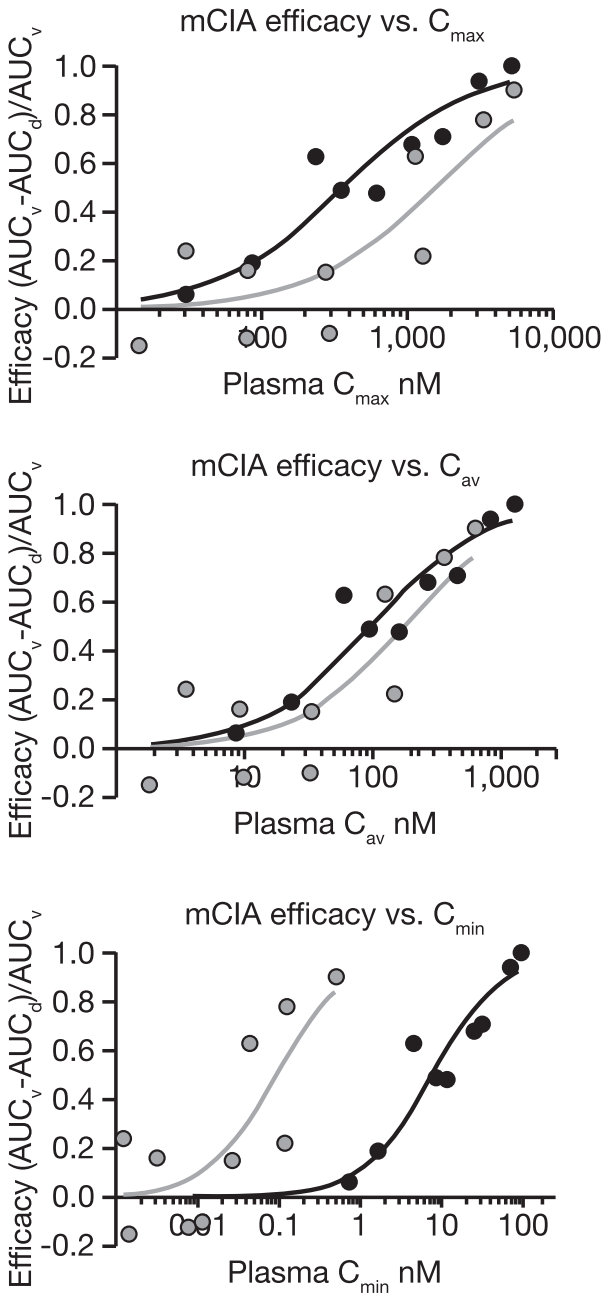

Figure 1 Tofacitinib exposure-response relationship in the mCIA inflammation model following q.d. and b.i.d. dosing regimens. Filled circles are mean efficacy and mean C_{max}, C_{av}, or C_{min} for individual cohorts (n = 10–15/dose group) of animals orally dosed q.d. (gray) and b.i.d. (black) with tofacitinib. Lines represent the best-fit nonlinear regression for q.d. (gray) and b.i.d. (black) administrations. The EC_{max50} values for the b.i.d. and q.d. regimens were 361 nM and 1,540 nM, respectively; corresponding values for EC_{av50} were 102 nM and 187 nM. The EC_{min50} values were 8.5 nM and 0.101 nM for the b.i.d. and q.d. regimens, respectively.
95% CI, 95% confidence interval; AUC_d, area under the concentration-severity curve for drug treatment; AUC_v, area under the concentration-severity curve for vehicle; b.i.d., twice daily; C_{av}, average drug concentration in the dosing interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; EC_{av50}, average concentration producing 50% of the maximal effect; EC_{max50}, maximum concentration producing 50% of the maximal effect; EC_{min50}, minimum concentration producing 50% of the maximal effect; mCIA, murine collagen-induced arthritis; nM, nanoMolar; q.d., once daily.

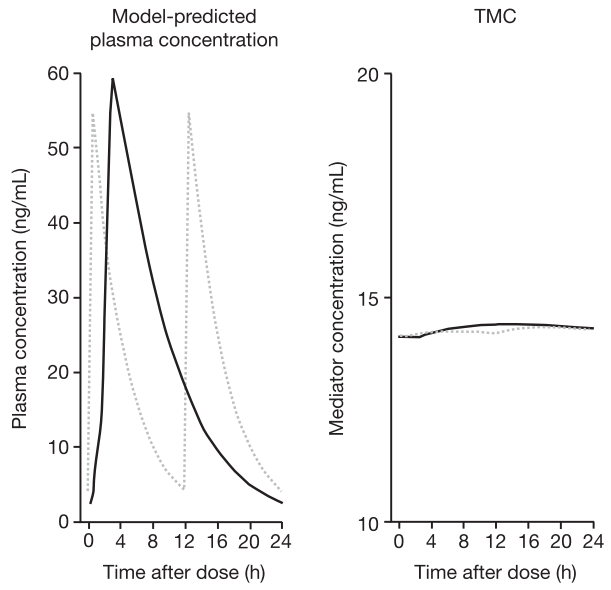

Figure 2 Predicted steady-state tofacitinib PK profile and TMC following IR 5 mg b.i.d. and XR 11 mg q.d. doses in RA patients. N = number of patients at each dose level. Solid and dashed lines represent XR 11 mg q.d. and IR 5 mg b.i.d., respectively. b.i.d., twice daily; h, hours; IR, immediate release; ng/mL, nanograms/milliliter; PK, pharmacokinetic; q.d., once daily; RA, rheumatoid arthritis; TMC, theoretical mediator concentrations; XR, extended release.

this observation, while the mean EC_{av50} (**Figure 1**) between q.d. and b.i.d. regimens was similar (187 nM vs. 102 nM, respectively), the corresponding values for C_{max} (EC_{max50}: 1,540 nM vs. 361 nM) and C_{min} (EC_{min50}: 0.10 nM vs. 8.5 nM) were discordant.

E-R evaluation of clinical data

Data from five phase II studies of the tofacitinib IR formulation in RA patients were included in E-R evaluations. These phase II data were used because they included several doses and dosing regimens, allowing better E-R characterization. Collectively, these analyses included data from ~1,350 patients with RA, encompassing a 30-fold dose range of tofacitinib IR (1–30 mg b.i.d. and 20 mg q.d.) and treatment durations ranging from 6–24 weeks.

Two well-validated clinical endpoints were included in the efficacy bridging analyses. Disease activity score using the 28-joint count (DAS28) is a continuous composite endpoint that measures joint tenderness, joint swelling, patient global assessment, and C-reactive protein as a laboratory marker of inflammation.[20] The American College of Rheumatology (ACR)-based responder rate is a categorical composite endpoint that includes physician- and patient-assessed components, as well as a laboratory test for inflammation.[21] Three ACR threshold values (ACR20, ACR50, and ACR70) are commonly used, reflecting the proportion of patients achieving 20, 50, or 70% improvement from baseline.

Characterization of delay in dynamics of efficacy response. A longitudinal DAS28 model, incorporating a hysteresis component, characterized the delay in the dynamics of DAS28 response. Onset rate of change in DAS28 was modeled as a function of dose. Details of the final model, including parameter estimates and visual predictive check (VPC) plots, are included in **Supplementary Section 1**. VPC evaluation showed that the model provided an adequate fit to the data. The onset half-life of DAS28 was estimated to be ~1 week for doses less than IR 5 mg b.i.d. and 3 weeks for IR 5 mg b.i.d.

Based on the estimated hysteresis function, which represents the delay due to distribution of the drug to the effect site and/or modulation of the biological cascade by tofacitinib, and consistent with an indirect response mechanism,[22] the DAS28 model was used to predict theoretical mediator concentrations (TMC) determining the clinical response to tofacitinib. This approach allowed visualization of the TMCs, which are in-phase with the PD effect, for the IR and XR formulations given the expected plasma concentration–time profiles. As shown in **Figure 2**, the TMCs (right panel) were nearly superimposable for IR 5 mg b.i.d. and XR 11 mg q.d.

Evaluation of efficacy of IR q.d. vs. IR b.i.d. regimens of tofacitinib. The importance of C_{min} to the efficacy of tofacitinib was tested using data from a phase II study (NCT00413660) in which RA patients received tofacitinib IR 1, 3, 5, 10, 15 mg b.i.d. or IR 20 mg q.d. or placebo. With the same total daily dose, AUC over 24 h was similar between IR 20 mg q.d. and IR 10 mg b.i.d. regimens. In contrast, C_{min} was ~7-fold (86%) lower and C_{max} ~2-fold higher for IR 20 mg q.d. relative to IR 10 mg b.i.d. Comparison of efficacy measures suggested similar efficacy[6] between the two regimens for both DAS28 change from baseline ((CFB) –1.72 for IR 20 mg q.d. vs. –1.82 for IR 10 mg b.i.d.) and ACR20/50/70 rates (56/36/24% for IR 20 mg q.d. vs. 58/28/12% for IR 10 mg b.i.d.).

A dose–response (D-R) model for b.i.d. doses at Week 12 (primary timepoint)[23] was constructed for DAS28, DAS28 CFB, and ACR response rates (see **Supplementary Table S1** for parameter estimates). The observed data for IR 20 mg q.d. was overlaid on the b.i.d. D-R curve to evaluate consistency in efficacy relative to the predicted b.i.d. D-R profile (**Figures 3, 4**). For both efficacy measures, IR 20 mg q.d. was well aligned with the b.i.d. D-R curves.

To further assess whether efficacy is consistent with AUC or C_{min}, the IR 20 mg q.d. ACR responses were plotted at two different locations on the x-axis: one corresponding to a total daily dose of 20 mg (gray square in the figure), and the other corresponding to a total daily dose of 2.8 mg (gray circle) to reflect the 7-fold lower C_{min} for IR 20 mg q.d. compared to IR 10 mg b.i.d. As shown in **Figure 4**, the gray squares (AUC) were within the prediction intervals (PIs) of the b.i.d. D-R curve on all three measures and consistent with AUC as the driver. On the other hand, the gray circles (C_{min}) were higher than would be predicted from the b.i.d. curves, particularly for ACR50 and 70, indicating that C_{min} is not predictive of the efficacy of tofacitinib.

Delineation of predictive abilities of C_{max}, C_{min}, and C_{av} for efficacy endpoints. The predictive abilities of tofacitinib exposure metrics were compared through an E_{max} model for DAS28 (**Table 1**) and an ordered categorical E_{max} model (**Table 2**) for ACR responses (see Methods).

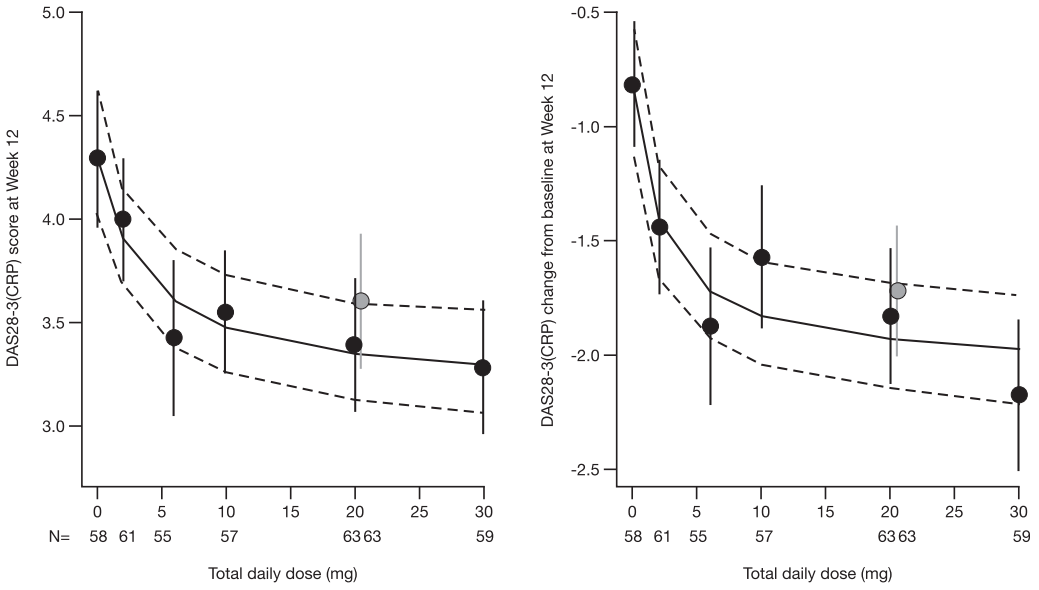

Figure 3 Dose–response relationship of DAS28 at Week 12 in RA patients receiving tofacitinib IR tablets as a b.i.d. regimen. X-axis shows tofacitinib dose on a total daily dose scale. Data for IR 20 mg q.d. and IR 10 mg b.i.d. are plotted at the same total daily location, with some spacing in between for resolution. Solid and dashed lines represent typical model prediction and 80% PI, respectively. Observed data (means) are shown by filled circles, with black circles for b.i.d. doses and gray for IR 20 mg q.d. dose. Error bars on filled circles are empirical 95% CIs. N, number of patients at each dose level; PI, prediction interval; b.i.d., twice daily; DAS28-3(CRP), disease activity score using 28-joint counts and C-reactive protein with three variables; IR, immediate release; mg, milligram; q.d., once daily; RA, rheumatoid arthritis.

For both efficacy measures, in the first stage of evaluation univariate analysis favored the C_{av} model compared with C_{max} or C_{min} models based on lowest Akaike Information Criterion (AIC) values.[24] Goodness-of-fit plots using C_{av}, C_{min}, or C_{max} as exposure metrics also confirmed better alignment of the endpoints with C_{av} as the predictor (**Supplementary Section 2**

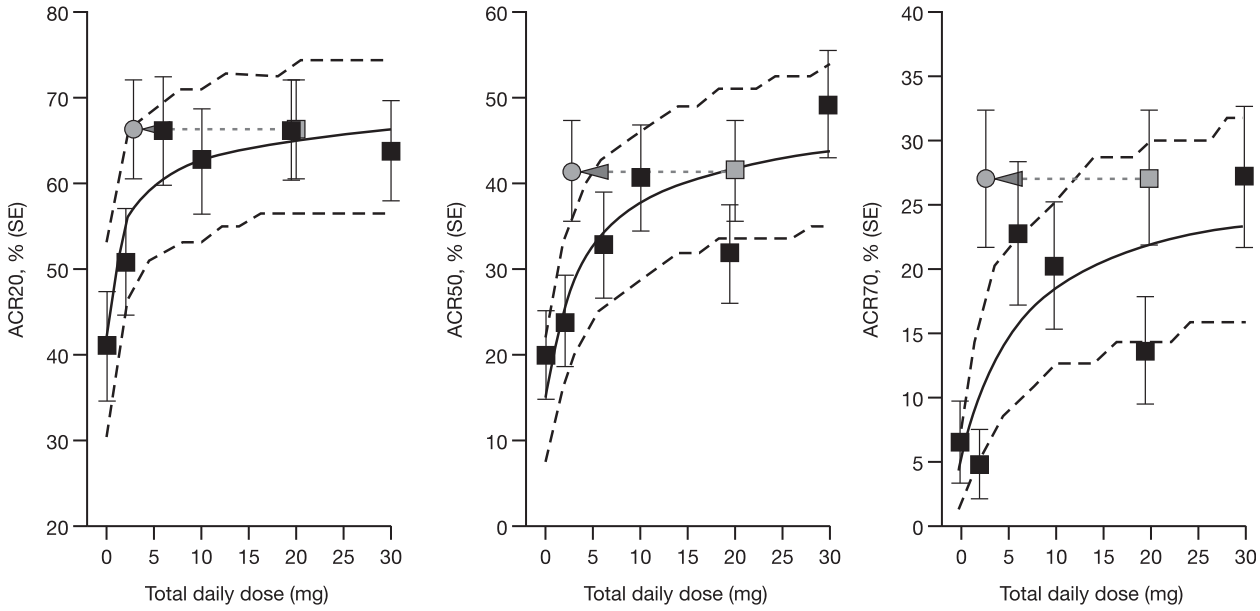

Figure 4 Dose–response relationship of proportion of ACR20/50/70 responders at Week 12 in RA patients receiving tofacitinib IR tablets as a b.i.d. regimen. Doses are presented on a total daily dose scale. Data for IR 20 mg q.d. and IR 10 mg b.i.d. are plotted at the same total daily location, with some spacing in between for resolution. Solid and dashed lines represent model-predicted posterior mean and 80% PI, respectively. Observed data (means) are shown by filled symbols, with black symbols for b.i.d. doses and gray for IR 20 mg q.d. dose. 20 mg q.d. data is placed either at an x-axis value of 20 (reflecting the same AUC_{24} as 10 mg b.i.d.) or at an x-axis value of 2.8 (reflecting the 86% lower C_{min} compared to 10 mg b.i.d.), respectively. The dashed arrow represents the comparison of responses based on AUC_{24} and C_{min} values for 20 mg q.d. regimen. %, percentage of responders; ACR, American College of Rheumatology; AUC_{24}, area under the concentration–time profile from time 0 to 24 h; b.i.d., twice daily; C_{min}, minimum plasma concentration; E_{max}, maximum drug effect; IR, immediate release; mg, milligrams; q.d., once daily; SE, standard error.

Table 1 Summary of E-R models for DAS28 at Week 12

Model ID[a]	Model parameters: PK predictor	Model parameters: PK parameter as covariate	AIC	OFV	Result
First stage					
AVG (Model 1)	C_{av}	NA	1,286.557	1,270.557	Model with C_{av} as the predictor has the lowest AIC
MAX (Model 2)	C_{max}	NA	1,294.381	1,278.381	Relative to Model 1, AIC ~8 point higher
MIN (Model 3)	C_{min}	NA	1,299.139	1,283.139	Relative to Model 1, AIC ~13 point higher
Second stage					
AVG-1 (Model 4)	C_{av}	C_{min} as covariate on EC_{50}	1,288.436	1,270.436	Relative to Model 1, OFV was essentially unchanged (ΔOFV = 0.121); addition of C_{min} as EC_{50} covariate to a C_{av}-only model did not show improvement.
AVG-2 (Model 5)	C_{av}	C_{min} as covariate on E_{max}	1,288.548	1,270.548	Relative to Model 1, OFV was essentially unchanged (ΔOFV = 0.009); addition of C_{min} as E_{max} covariate to a C_{av}-only model did not show improvement.
Third stage (sensitivity analysis)					
MIN-1 (Model 6)	C_{min}	C_{av} as covariate on EC_{50}	1,295.499	1,277.499	Relative to Model 3, ΔOFV = 5.640 decrease; addition of C_{av} as EC_{50} covariate to a C_{min}-only model showed improvement.
MIN-2 (Model 7)	C_{min}	C_{av} as covariate on E_{max}	1,299.045	1,281.045	Relative to Model 3, ΔOFV = 2.094 decrease; addition of C_{av} as E_{max} covariate to a C_{min}-only model did not show improvement.

AIC, Akaike Information Criterion; C_{av}, average drug concentration in the dosing interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; DAS28, disease activity score using 28-joint counts; E_{max}, maximum drug effect; EC_{50}, concentration producing 50% of the maximum effect; E-R, exposure response; ID, identification; NA, not applicable; OFV, objective function value (-2LogLikelihood); PK, pharmacokinetic; ΔOFV, difference in OFV between reduced and test model; χ^2, chi-square.

[a]Model ID is provided to facilitate differentiation between models appearing in this table. Significance was assessed by comparing ΔOFV against a χ^2 distribution with one degree of freedom. This critical χ^2 value is 3.84 and is equivalent to a *P*-value of 0.05.

for ACR response rates; figure not shown for DAS28). Because of C_{min} differences between XR and IR formulations of tofacitinib, further analyses focused on evaluating the added value of C_{min} over and above C_{av}.

In the second stage, the objective function value (OFV) for models in which C_{min} was additionally included as a covariate on E_{max} or concentration producing 50% of the maximum effect (EC_{50}) were not significantly different from C_{av}-only model; 90% confidence interval (CI) for the C_{min} covariate effect also included zero (**Supplementary Table S2 and Supplementary Section 2**). These results indicated that adding C_{min} as a covariate did not offer any additional improvement over a C_{av}-only model. Finally, in the sensitivity analyses (3rd stage), the addition of C_{av} as a covariate on E_{max} or EC_{50} to a model with C_{min} as the predictor yielded significant improvements, compared with C_{min} alone for ACR response rates (**Table 3**), even with the observed correlation of 0.79 between C_{av} and C_{min}. For DAS28, inclusion of C_{av} as a covariate on EC_{50} decreased OFV significantly, while the addition of C_{av} as a covariate on E_{max} did not (**Table 2**).

Taken together, the results demonstrated that C_{av} (or AUC) is the most predictive drug-exposure measure of tofacitinib efficacy and that C_{min} did not provide additional predictive value over and above that of C_{av}.

DISCUSSION

The purpose of the current investigation was to use an E-R modeling approach to inform the development and US registration of the tofacitinib XR formulation administered q.d. From a mechanistic standpoint, tofacitinib as a JAK inhibitor blocks signaling through the common gamma chain of the surface receptors for several cytokines that are central to the pathogenesis of RA, including interleukins (IL)-7, -15, and -21.[25,26] It also attenuates signaling by proinflammatory cytokines such as IL-6 and interferon. Because cytokine signaling promotes disease through the recruitment and activation of effector cells at sites of pathologic inflammation,[27] the pharmacological effect of tofacitinib on clinical endpoints resulting from inhibition of cytokine signaling is indirect. This provides a sound scientific basis to expect that the clinical endpoints would not be significantly influenced by short-term fluctuations in plasma concentrations within the dosing interval, but instead would be dependent on the overall average exposure over a period of time (e.g., weeks to months), as measured by AUC (or C_{av}).[1] This hypothesis is supported by the clinical data from the IR RA development program as well as the nonclinical data, as described below.

Results from the nonclinical analyses showed concordance of E-R curves and EC_{50} values using C_{av} (ratio of EC_{50} values (q.d./b.i.d.) ~1.8), and divergence with either C_{max} (~4.3) or

Table 2 Summary of E-R Models for ACR response rates at Week 12

Model ID[a]	Model parameters: PK parameter	Model parameters: Secondary parameter as covariate	AIC	OFV	Results
First stage					
AVG (Model 1)	C_{av}	NA	2,371.987	2,337.987	Model with C_{av} as the predictor has the lowest AIC
MAX (Model 2)	C_{max}	NA	2,374.001	2,340.001	Relative to Model 1, AIC ~2 points greater
MIN (Model 3)	C_{min}	NA	2,399.066	2,365.066	Relative to Model 1, AIC ~27 points greater
Second stage					
AVG-1 (Model 4)	C_{av}	C_{min} as covariate on EC_{50}	2,373.986	2,337.986	Relative to Model 1, OFV was essentially unchanged (ΔOFV = 0.001); addition of C_{min} as EC_{50} covariate to a C_{av}-only model did not show improvement.
AVG-2 (Model 5)	C_{av}	C_{min} as covariate on E_{max}	2,373.908	2,337.908	Relative to Model 1, OFV was essentially unchanged (ΔOFV = 0.079); addition of C_{min} as E_{max} covariate to a C_{av}- only model did not show improvement.
Third stage (sensitivity analysis)					
MIN-1 (Model 6)	C_{min}	C_{av} as covariate on EC_{50}	2,390.001	2,354.001	Relative to Model 3, ΔOFV = 11.065 decrease; addition of C_{av} as EC_{50} covariate to a C_{min}-only model showed improvement.
MIN-2 (Model 7)	C_{min}	C_{av} as covariate on E_{max}	2,393.041	2,357.041	Relative to Model 3, ΔOFV = 8.025 decrease; addition of C_{av} as E_{max} covariate to a C_{min} -only model showed improvement.

AIC, Akaike Information Criterion; ACR, American College of Rheumatology; C_{av}, average drug concentration in the dosing interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; E_{max}, maximum drug effect; EC_{50}, concentration producing 50% of the maximum effect; E-R, exposure-response; ID, identification; NA, not applicable; OFV, objective function value (-2LogLikelihood); PK, pharmacokinetic; ΔOFV, difference in OFV between reduced and test model; χ^2, chi square.
[a]Model ID is provided to facilitate differentiation between models appearing in this table. Significance was assessed by comparing ΔOFV against a χ^2 distribution with one degree of freedom. This critical χ^2 value is 3.84 and is equivalent to a *P*-value of 0.05.

C_{min} (~84), supporting the relevance of C_{av} in predicting nonclinical antiinflammatory activity. The mCIA model has proven useful in the screening and development of new therapies for treatment of RA[28] and has allowed quantitative E-R analyses for a number of approved RA therapies with a wide array of mechanisms (methotrexate,[29] abatacept,[30] anakinra,[31] etanercept,[32] glucocorticoids[33–36]). The dose fractionation technique that was employed in this experiment has been successfully used in other therapeutic areas[37,38] to delineate the relative effect of various PK parameters on response.

E-R characterization from clinical data provides further evidence of the importance of C_{av} to tofacitinib efficacy. From the DAS28 hysteresis model in RA patients, a 3-week onset half-life was estimated for IR 5 mg b.i.d., indicating achievement of PD steady state in weeks compared to achievement of PK steady state within 24–48 h. Consistent with the delay, the TMC profiles were essentially superimposable between the XR and IR formulations, suggesting that within-day fluctuations in the PK profile of tofacitinib are unlikely to confer differential effectiveness.

Clinical data from a phase IIB double-blind study, which included tofacitinib IR 20 mg q.d. and several tofacitinib IR b.i.d. doses (1–15 mg), support the indirect response dynamics. The efficacy of IR 20 mg q.d. was similar to IR 10 mg b.i.d. across various clinical domains and consistent with the b.i.d. D-R profiles across these endpoints. Importantly, the two 20 mg total daily dose IR regimens achieved similar AUC over 24 h but with large differences in the shape of the concentration–time course, resulting in 7-fold (86%) lower C_{min} and 2-fold higher C_{max} for IR 20 mg q.d. compared to IR 10 mg b.i.d.

Efficacy characterization from this study was limited by the use of a 2-fold higher dose (IR 20 mg q.d.) compared to the approved dose (IR 5 mg b.i.d.), the relatively shallow shape of the b.i.d. dose response in this dose range, and the 2-fold higher C_{max} compared to IR 10 mg b.i.d. However, if C_{min} were the driver, the resulting efficacy would have been similar to that of ~IR 3 mg b.i.d., a dose with a low probability of achieving clinically meaningful responses, particularly on stringent measures of efficacy such as ACR50 and ACR70.[39] Since the ACR data showed similar efficacy between IR 20 mg q.d. and 10 mg b.i.d., it can be concluded that C_{max} or C_{min} differences were not meaningful.

The efficacy bridging was substantiated by comparison of goodness-of-fit characteristics between PK parameters of tofacitinib. For both DAS28 and ACR response rates, models using C_{av} had the lowest OFV and AIC values, and the addition of C_{min} as a covariate on E_{max} or EC_{50} showed no added value compared to the C_{av}-only model. In contrast, the addition of C_{av} as a covariate of EC_{50} to a model using C_{min} as a predictor yielded statistically significant improvements for both efficacy measures. Additionally, improvements in OFV were also noted when C_{av} was added as a covariate on E_{max} for the ACR model.

Table 3 Characteristics of tofacitinib IR phase II studies in RA included in the E-R analyses

Clinical Trials.gov identifier	Pfizer study number	Treatments/tofacitinib IR doses	Number of patients	Treatment duration (weeks)	Analysis		
					Characterization of delay in dynamics of efficacy response	Evaluation of efficacy of IR q.d. vs. IR b.i.d. regimens of tofacitinib	Delineation of predictive abilities of C_{max}, C_{min}, and C_{av} for efficacy endpoints
NCT00147498	A3921019	PBO and 5, 15, or 30 mg b.i.d.	264	6	✓	–	–
NCT00413660	A3921025	PBO and 1, 3, 5, 10, or 15 mg b.i.d. or 20 mg q.d.	507	24	✓	✓	✓
NCT00550446	A3921035	PBO and 1, 3, 5, 10, or 15 mg b.i.d.	384	24	✓	–	✓
NCT00603512	A3921039	PBO and 1, 3, 5, or 10 mg b.i.d. (Japanese patients)	161	12	✓	–	✓
NCT00687193	A3921040	PBO and 1, 3, 5, 10, or 15 mg b.i.d. in (Japanese patients)	317	12	✓	–	✓

b.i.d., twice daily; C_{av}, average drug concentration in the dosing interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; E-R, exposure-response; IR, immediate release; PBO, placebo; q.d., once daily; RA, rheumatoid arthritis.

Taken together, the three-stage analysis established C_{av} as the better predictor of efficacy than C_{min} or C_{max}.

In summary, application of E-R approaches from different data sources demonstrated consistently that tofacitinib AUC (or C_{av}) is the most relevant drug-exposure parameter for efficacy and that the 29% lower C_{min} with tofacitinib XR is not clinically important to the efficacy of tofacitinib. This is supported by the observed delay in clinical response dynamics relative to PK; the similar clinical efficacy observed with IR 20 mg q.d. and IR 10 mg b.i.d. doses, despite a large difference in C_{min}; the improved goodness-of-fit characteristics with C_{av} compared to C_{max} or C_{min}; and the corroborative evidence from nonclinical dose fractionation data.

Given the PK profile of the XR formulation, which included equivalence on AUC and C_{max}, and ~29% lower C_{min} relative to the IR formulation, the primary focus of our analyses was to bridge efficacy between the XR and IR formulations. Considering these PK characteristics, the safety profile of the XR formulation is also expected to be consistent with the IR formulation, given the similar or slightly lower systemic exposure parameters. Additionally, the expected duration of steady-state plasma concentrations above the *in vitro*, whole-blood concentration producing 50% of the maximum inhibition for JAK 1/3 signaling (17 ng/mL) is ~12–13 h for both formulations over a 24-hour period (Pfizer data on file), suggesting a similar level of target enzyme inhibition over the dosing interval.

On the basis of the demonstrated equivalence in AUC between the two formulations and the evidence from E-R relationships that AUC is the relevant parameter for clinical response, tofacitinib XR 11 mg q.d. was granted regulatory approval by the FDA without the need for a phase III trial. Our analyses illustrate the potential of robust D-R studies and E-R relationships to not only facilitate efficient drug development for alternative formulations/doses/regimens but also provide evidence sufficient to obviate the need for confirmatory clinical trials.

METHODS

Modeling nonclinical efficacy data

Fixed total daily doses of tofacitinib (1, 3, 10, 30, and 100 mg/kg) and vehicle control were administered orally in q.d. and b.i.d. dosing frequencies to male Harlan Sprague-Dawley mice (n = 10–15/treatment group) after a boost of collagen, as described previously by Dowty *et al.*[19] Arthritis severity scores were measured at the start of the study and postboost of collagen on Day 21. Sparse PK samples were collected from all treatment groups.

Efficacy was assessed by area under the severity score time-course (AUEC). Mean AUEC for each treatment group was subtracted from that of the respective mean vehicle control and standardized with the vehicle control to yield a fractional AUEC. Utilizing a one-compartment PK model, AUC from time 0 to 24 h and PK parameters including C_{av}, C_{max}, and C_{min} were determined. Mean fractional AUEC for each treatment group was modeled as a function of mean PK parameters using a standard E_{max} model (GraphPad Prism, GraphPad Software, La Jolla, CA).

E-R evaluation of clinical data

Clinical studies and endpoints. Analyses of clinical efficacy utilized data from up to five phase II randomized, placebo-controlled, double-blind

studies from the tofacitinib IR development program.[4–8] All studies were approved by the Institutional Review Boards (IRBs) and/or Independent Ethics Committees of each investigational center or a central IRB. The studies were conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. All patients provided written informed consent. Pertinent features of the five phase II studies included in the E-R analyses are provided in **Table 3**.

Characterization of delay in dynamics of efficacy response. Pooled data from five phase II studies (**Table 3**) were used for longitudinal DAS28 modeling. Using an E_{max} structure form, the model was parameterized on an exponential scale to ensure individual predictions were >0, as outlined below:

$$DAS28(t) = \exp\left(Base + Placebo(t) + \frac{E_{\max} \cdot S(t)}{S(t) + E_{50}}\right) + g \cdot \varepsilon$$

where *Base* is the baseline function of parameters; *Placebo* (*t*) represents the nondrug function of parameters when exposure is 0; *S(t)* refers to the mediator concentrations that are in-phase with the drug effect at time *t*; E_{max} represents the maximum drug effect; E_{50} is the *S(t)* that achieves $^1/_2$ E_{max}; *g* represents the residual variance function by study; and ε is the residual random effect assumed to be normally distributed with mean of 0 and variance of 1. Additive intersubject variability was included on baseline, placebo, and drug-effect parameters. Onset of drug effect or hysteresis was evaluated by inclusion of a dose-dependent rate constant. NONMEM versions 7.2.0 and 7.3 (ICON Development Solutions, Ellicott City, MD), using the Laplace approximation was implemented. The population mean and 10th and 90th percentiles of simulated DAS28 were computed for each replicate, followed by PIs for each of these three statistics across the trial replicates via VPC.[40] Model performance was determined by agreement between the 80% PIs and the observed statistics across studies and doses.

PK profiles for the XR and IR formulations were predicted using a population PK model (clearance (20.6 L/h), volume (90.2 L)) in RA patients and absorption parameters (0.189 h and 0.34 h for XR and IR formulations, respectively).[41] A 9% estimated reduction in relative bioavailability (F_{rel} = 0.912) for the XR formulation relative to the IR was applied. The hysteresis parameter estimated from the DAS28 model was linked to the PK model to yield the TMC profile for each formulation.

Evaluation of efficacy of IR q.d. vs. IR b.i.d. regimens of tofacitinib. A D-R model at Week 12 was constructed for DAS28 and ACR efficacy measures to evaluate the consistency of the efficacy of IR 20 mg q.d. relative to the b.i.d. dose–response curves. For DAS28, a nonlinear E_{max} model with additive residual error was fitted to DAS28 and DAS28 CFB. Maximum likelihood estimation, as implemented in PROC NLMIXED (SAS, Cary, NC), was used. A previously described Bayesian ACR longitudinal dose–response model was implemented for ACR response rates.[42] The model is an extension of the three-parameter E_{max} model with parameters (maximum drug effect: E_{max}; dose producing 50% of the maximum effect: ED_{50} (measure of potency); placebo response: P0) that can change as functions of time. For both endpoints, data from b.i.d. doses were used for developing the model; IR 20 mg q.d. was overlaid on the model-predicted b.i.d. dose–response profile.

Delineation of predictive abilities of C_{max}, C_{min}, and C_{av} for efficacy endpoints. To characterize the most relevant tofacitinib PK parameter for efficacy and assess the predictive value of C_{min} over and above C_{av}, efficacy data at Week 12 from four phase II studies were analyzed. Steady-state subject-specific PK parameters (C_{av}, C_{max}, and C_{min}) were predicted from a population PK model in RA patients.[41] For DAS28, a standard E_{max} model was developed. The three ACR endpoints (20/50/70) were jointly modeled using a four-category response model (ACR20 nonresponder, ACR20 but not ACR50 responder, ACR50 but not ACR70 responder, and ACR70 responder) represented by values of 0, 1, 2, and 3, respectively (see **Supplementary Section 2**). The ordered categorical approach utilizes information from ACR20, ACR50, and ACR70 endpoints in a simultaneous approach compared to individual binary models resulting in improved precision of common parameters (e.g., EC_{50}) of the E-R model.[43] The models were fitted using maximum likelihood estimation of the NLMIXED procedure in SAS v. 9.3.

Model testing was conducted in three stages. In Stage 1, each exposure metric was individually tested as the predictor in the E-R model. In Stage 2, C_{min} was added to the E-R model as a covariate of E_{max} or EC_{50} to a model having C_{av} as the predictor, to evaluate if C_{min} had any added predictive value over and above C_{av}. In Stage 3, a sensitivity analysis was conducted by reversing the order of testing, whereby C_{min} was set as the predictor and C_{av} was included as a covariate on E_{max} or EC_{50}. The general form of the equation for Stages 2 and 3 is shown below:

$$D = \theta_D \cdot [1 + \theta_P(P - median(P))]$$

where $\boldsymbol{D}$ is the drug-effect parameter $\theta_{\boldsymbol{D}}$ (E_{max} or EC_{50}); $\theta_{\boldsymbol{P}}$ is the fractional change in $\boldsymbol{D}$; $\boldsymbol{P}$ is the PK parameter (C_{av} or C_{min}). Models were compared based on AIC (Stage 1, comparing non-nested models) and OFV (Stages 2 and 3, comparing nested models) at a significance level of 0.05 (Δ OFV $\geq$3.84). Consideration was also given to goodness-of-fit plots, and CIs of the covariate effect on parameters.

Additional Supporting Information may be found in the online version of this article.

ACKNOWLEDGMENTS

This study was sponsored by Pfizer Inc. Editorial support was provided by Anne Marie Reid, PhD, at Complete Medical Communications and was funded by Pfizer Inc.

CONFLICT OF INTEREST/DISCLOSURE

M.L., M.E.D., C.N., T.S., J.C., and S.K. are employees and shareholders of Pfizer Inc. M.H. has acted as a consultant for Pfizer Inc. D.C. was an employee of Pfizer Inc at the time these analyses were conducted. D.E.F. has received research support and is a consultant for Pfizer Inc. A.D. is a consultant and member of speakers' bureaus for AbbVie and Pfizer Inc.

AUTHOR CONTRIBUTIONS

S.K., M.L., M.M.H., D.E.F., A.D., M.E.D., D.C., T.S., C.N., and J.C. wrote the article; S.K., M.L., M.M.H., D.E.F., A.D., M.E.D., D.C., T.S., C.N., and J.C. designed the research; S.K., M.L., M.M.H., D.E.F.,, A.D., M.E.D., D.C., T.S., C.N., and J.C. performed the research; S.K., M.L., M.M.H., D.E.F., M.E.D., D.C., T.S., C.N., and J.C. analyzed the data.

1. Chen, M.L. *et al*. Challenges and opportunities in establishing scientific and regulatory standards for assuring therapeutic equivalence of modified release products: workshop summary report. *AAPS. J.* **12**, 371–377 (2010).
2. FDA. Guidance for industry. Providing clinical evidence of effectiveness for human drug and biological products. <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>. Last updated 1998; Accessed 14 June 2016.
3. McInnes, I.B. & Schett, G. The pathogenesis of rheumatoid arthritis. *N. Engl. J. Med.* **365**, 2205–2219 (2011).
4. Fleischmann, R. *et al*. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an

inadequate response to disease-modifying antirheumatic drugs. *Arthritis Rheum.* **64**, 617–629 (2012).
5. Kremer, J.M. *et al*. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. *Arthritis Rheum.* **60**, 1895–1905 (2009).
6. Kremer, J.M. *et al*. A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum.* **64**, 970–981 (2012).
7. Tanaka, Y., Suzuki, M., Nakamura, H., Toyoizumi, S., Zwillich, S.H. & Tofacitinib Study Investigators. Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res. (Hoboken)* **63**, 1150–1158 (2011).
8. Tanaka, Y., Takeuchi, T., Yamanaka, H., Nakamura, H., Toyoizumi, S. & Zwillich, S. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. *Mod. Rheumatol.* **25**, 514–521 (2015).
9. Burmester, G.R. *et al*. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet* **381**, 451–460 (2013).
10. Fleischmann, R. *et al*. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N. Engl. J. Med.* **367**, 495–507 (2012).
11. Kremer, J. *et al*. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. *Ann. Intern. Med.* **159**, 253–261 (2013).
12. Lee, E.B. *et al*. Tofacitinib versus methotrexate in rheumatoid arthritis. *N. Engl. J. Med.* **370**, 2377–2386 (2014).
13. van der Heijde, D. *et al*. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum.* **65**, 559–570 (2013).
14. van Vollenhoven, R.F. *et al*. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N. Engl. J. Med.* **367**, 508–519 (2012).
15. Wollenhaupt, J. *et al*. Safety and efficacy of tofacitinib, an oral Janus kinase Inhibitor, for the treatment of rheumatoid arthritis in open-label, longterm extension studies. *J. Rheumatol.* **41**, 837–852 (2014).
16. Coleman, C.I. *et al*. Dosing frequency and medication adherence in chronic disease. *J. Manag. Care Pharm.* **18**, 527–539 (2012).
17. Saini, S.D., Schoenfeld, P., Kaulback, K. & Dubinsky, M.C. Effect of medication dosing frequency on adherence in chronic diseases. *Am. J. Manag. Care* **15**, e22–e33 (2009).
18. Lamba, M., Wang, R., Fletcher, T., Alvey, C., Kushner, J. & Stock, T.C. Extended-release once-daily formulation of tofacitinib: evaluation of pharmacokinetics compared with immediate-release tofacitinib and impact of food. *J. Clin. Pharmacol.* **56**, 1362–1371 (2016).
19. Dowty, M.E. *et al*. Preclinical to clinical translation of tofacitinib, a Janus kinase inhibitor, in rheumatoid arthritis. *J. Pharmacol. Exp. Ther.* **348**, 165–173 (2014).
20. van Gestel, A.M., Haagsma, C.J. & van Riel, P.L. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. *Arthritis Rheum.* **41**, 1845–1850 (1998).
21. Felson, D.T. *et al*. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* **38**, 727–735 (1995).
22. Dayneka, N.L., Garg, V. & Jusko, W.J. Comparison of four basic models of indirect pharmacodynamic responses. *J. Pharmacokinet. Biopharm.* **21**, 457–478 (1993).
23. FDA. Guidance for industry rheumatoid arthritis: developing drug products for treatment. <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>. Last updated 2013; Accessed 14 June 2016.
24. Cavanaugh, J.E. Akaike Information Criterion. <http://sk.sagepub.com/reference/statistics/n9.xml>. Last updated 2007; Accessed 14 June 2016.
25. Meyer, D.M. *et al*. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. *J. Inflamm. (Lond).* **7**, 41 (2010).
26. Hodge, J.A. *et al*. The mechanism of action of tofacitinib — an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. *Clin. Exp. Rheumatol.* **34**, 318–328 (2016).
27. McInnes, I.B. & Liew, F.Y. Cytokine networks — towards new therapies for rheumatoid arthritis. *Nat. Clin. Pract. Rheumatol.* **1**, 31–39 (2005).
28. Kannan, K., Ortmann, R.A. & Kimpel, D. Animal models of rheumatoid arthritis and their relevance to human disease. *Pathophysiology* **12**, 167–181 (2005).
29. Liu, D.Y., Lon, H.K., Wang, Y.L., DuBois, D.C., Almon, R.R. & Jusko, W.J. Pharmacokinetics, pharmacodynamics and toxicities of methotrexate in healthy and collagen-induced arthritic rats. *Biopharm. Drug Dispos.* **34**, 203–214 (2013).
30. Lon, H.K., Liu, D., DuBois, D.C., Almon, R.R. & Jusko, W.J. Modeling pharmacokinetics/pharmacodynamics of abatacept and disease progression in collagen-induced arthritic rats: a population approach. *J. Pharmacokinet. Pharmacodyn.* **40**, 701–712 (2013).
31. Liu, D., Lon, H.K., DuBois, D.C., Almon, R.R. & Jusko, W.J. Population pharmacokinetic-pharmacodynamic-disease progression model for effects of anakinra in Lewis rats with collagen-induced arthritis. *J. Pharmacokinet. Pharmacodyn.* **38**, 769–786 (2011).
32. Lon, H.K., Liu, D., Zhang, Q., DuBois, D.C., Almon, R.R. & Jusko, W.J. Pharmacokinetic-pharmacodynamic disease progression model for effect of etanercept in Lewis rats with collagen-induced arthritis. *Pharm. Res.* **28**, 1622–1630 (2011).
33. Earp, J.C., DuBois, D.C., Molano, D.S., Pyszczynski, N.A., Almon, R.R. & Jusko, W.J. Modeling corticosteroid effects in a rat model of rheumatoid arthritis II: mechanistic pharmacodynamic model for dexamethasone effects in Lewis rats with collagen-induced arthritis. *J. Pharmacol. Exp. Ther.* **326**, 546–554 (2008).
34. Earp, J.C., Pyszczynski, N.A., Molano, D.S. & Jusko, W.J. Pharmacokinetics of dexamethasone in a rat model of rheumatoid arthritis. *Biopharm. Drug Dispos.* **29**, 366–372 (2008).
35. Earp, J.C. *et al*. Modeling corticosteroid effects in a rat model of rheumatoid arthritis I: mechanistic disease progression model for the time course of collagen-induced arthritis in Lewis rats. *J. Pharmacol. Exp. Ther.* **326**, 532–545 (2008).
36. Earp, J.C., DuBois, D.C., Almon, R.R. & Jusko, W.J. Quantitative dynamic models of arthritis progression in the rat. *Pharm. Res.* **26**, 196–203 (2009).
37. Jumbe, N.L. *et al*. Modeling the efficacy of trastuzumab-DM1, an antibody drug conjugate, in mice. *J. Pharmacokinet. Pharmacodyn.* **37**, 221–242 (2010).
38. Tuntland, T. *et al*. Implementation of pharmacokinetic and pharmacodynamic strategies in early research phases of drug discovery and development at Novartis Institute of Biomedical Research. *Front. Pharmacol.* **5**, 174 (2014).
39. Milligan, P.A. *et al*. Model-based drug development: a rational approach to efficiently accelerate drug development. *Clin. Pharmacol. Ther.* **93**, 502–514 (2013).
40. Karlsson, M.O. & Holford, N. A tutorial on visual predictive checks. Abstract presented at the 17th Annual Meeting of the Population Approach Group in Europe 2008.
41. FDA Center for Drug Evaluation and Research. Clinical Pharmacology and Biopharmaceutics Review of Tofacitinib. NDA203214. <http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203214Orig1s000ClinPharmR.pdf>. Last updated 21 October 2011; Accessed 14 June 2016.
42. Tan, H., Gruben, D., French, J. & Thomas, N. A case study of model-based Bayesian dose response estimation. *Stat. Med.* **30**, 2622–2633 (2011).
43. Lacroix, B.D., Karlsson, M.O. & Friberg, L.E. Simultaneous exposure-response modeling of ACR20, ACR50, and ACR70 improvement scores in rheumatoid arthritis patients treated with certolizumab pegol. *CPT Pharmacometrics Syst. Pharmacol.* **3**, e143 (2014).