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

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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,
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\(_{\text{max}}\)) of XR 11 mg q.d. compared to IR 5 mg b.i.d. At steady state, minimum plasma concentration (C\(_{\text{min}}\)) 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\(_{\text{max}}\) or C\(_{\text{min}}\)) that was most relevant for efficacy and evaluate the clinical relevance of differences in C\(_{\text{min}}\) 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\(_{\text{min}}\) 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\(_{\text{max}}\)) 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\(_{\text{max}50}\)), average concentration producing 50% of the maximal effect (EC\(_{\text{av}50}\)), minimum concentration producing 50% of the maximal effect (EC\(_{\text{min}50}\))) 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\(_{\text{av}}\)) which offers the same interpretation as AUC since C\(_{\text{av}}\) is proportionally related to AUC as AUC/dosing interval was used as the predictor of response. In contrast, significant divergence was observed when C\(_{\text{max}}\) or C\(_{\text{min}}\) was used as the predictor. Supporting
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 efficacy6 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 E_{max} 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).
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. 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).

![Diagrams](Figure 3 and Figure 4)
for ACR response rates; figure not shown for DAS28). Because of $C_{\text{min}}$ differences between XR and IR formulations of tofacitinib, further analyses focused on evaluating the added value of $C_{\text{min}}$ over and above $C_{av}$.

In the second stage, the objective function value (OFV) for models in which $C_{\text{min}}$ was additionally included as a covariate on $E_{\text{max}}$ 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 $C_{\text{min}}$ covariate effect also included zero (Supplementary Table S2 and Supplementary Section 2). These results indicated that adding $C_{\text{min}}$ 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 $E_{\text{max}}$ or $EC_{50}$ to a model with $C_{\text{min}}$ as the predictor yielded significant improvements, compared with $C_{\text{min}}$ alone for ACR response rates (Table 3), even with the observed correlation of 0.79 between $C_{av}$ and $C_{\text{min}}$. 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 $E_{\text{max}}$ 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 $C_{\text{min}}$ 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 $C_{\text{max}}$ (~4.3) or

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

| Model IDa | PK predictor | 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) | $C_{\text{max}}$ | NA                        | 1,294.381 | 1,278.381 | Relative to Model 1, AIC ~8 point higher |
| MIN (Model 3) | $C_{\text{min}}$ | NA                        | 1,299.139 | 1,283.139 | Relative to Model 1, AIC ~13 point higher |
| **Second stage**                        |               |                           |       |       |                                             |
| AVG-1 (Model 4) | $C_{av}$ | $C_{\text{min}}$ as covariate on $EC_{50}$ | 1,288.436 | 1,270.436 | Relative to Model 1, OFV was essentially unchanged ($\Delta$OFV = 0.121); addition of $C_{\text{min}}$ as $EC_{50}$ covariate to a $C_{av}$-only model did not show improvement. |
| AVG-2 (Model 5) | $C_{av}$ | $C_{\text{min}}$ as covariate on $E_{\text{max}}$ | 1,288.548 | 1,270.548 | Relative to Model 1, OFV was essentially unchanged ($\Delta$OFV = 0.009); addition of $C_{\text{min}}$ as $E_{\text{max}}$ covariate to a $C_{av}$-only model did not show improvement. |
| **Third stage (sensitivity analysis)** |               |                           |       |       |                                             |
| MIN-1 (Model 6) | $C_{\text{min}}$ | $C_{av}$ as covariate on $EC_{50}$ | 1,295.499 | 1,277.499 | Relative to Model 3, $\Delta$OFV = 5.640 decrease; addition of $C_{av}$ as $EC_{50}$ covariate to a $C_{\text{min}}$-only model showed improvement. |
| MIN-2 (Model 7) | $C_{\text{min}}$ | $C_{av}$ as covariate on $E_{\text{max}}$ | 1,299.045 | 1,281.045 | Relative to Model 3, $\Delta$OFV = 2.094 decrease; addition of $C_{av}$ as $E_{\text{max}}$ covariate to a $C_{\text{min}}$-only model did not show improvement. |

AIC, Akaike Information Criterion; $C_{av}$, average drug concentration in the dosing interval; $C_{\text{max}}$, maximum plasma concentration; $C_{\text{min}}$, minimum plasma concentration; DAS28, disease activity score using 28-joint counts; $E_{\text{max}}$, 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; $\Delta$OFV, difference in OFV between reduced and test model; $\chi^2$, chi-square.

aModel ID is provided to facilitate differentiation between models appearing in this table. Significance was assessed by comparing $\Delta$OFV against a $\chi^2$ distribution with one degree of freedom. This critical $\chi^2$ value is 3.84 and is equivalent to a $P$-value of 0.05.
Table 2 Summary of E-R Models for ACR response rates at Week 12

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

AIC, Akaike Information Criterion; ACR, American College of Rheumatology; C<sub>av</sub>, average drug concentration in the dosing interval; C<sub>max</sub>, maximum plasma concentration; C<sub>min</sub>, minimum plasma concentration; E<sub>max</sub>, maximum drug effect; EC<sub>50</sub>, 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<sup>2</sup>, chi square.

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

dose IR regimes 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<sub>min</sub> and 2-fold higher C<sub>max</sub> 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<sub>max</sub> compared to IR 10 mg b.i.d. However, if C<sub>min</sub> 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<sub>max</sub> or C<sub>min</sub> 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<sub>av</sub> had the lowest OFV and AIC values, and the addition of C<sub>min</sub> as a covariate on E<sub>max</sub> or EC<sub>50</sub> showed no added value compared to the C<sub>av</sub>-only model. In contrast, the addition of C<sub>av</sub> as a covariate of EC<sub>50</sub> to a model using C<sub>min</sub> as a predictor yielded statistically significant improvements for both efficacy measures. Additionally, improvements in OFV were also noted when C<sub>av</sub> was added as a covariate on E<sub>max</sub> for the ACR model.
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
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 $E_{\text{max}}$ structure form, the model was parameterized on an exponential scale to ensure individual predictions were $>0$, as outlined below:

$$D\text{AS28}(t)=\exp\left(\text{Base}+\text{Placebo}(t)+\frac{E_{\text{max}} \cdot S(t)}{S(t)+E_0}\right)+g \cdot \varepsilon$$

where $\text{Base}$ is the baseline function of parameters; $\text{Placebo}(t)$ 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 $t$; $E_{\text{max}}$ represents the maximum drug effect; $E_0$ is the $S(t)$ that achieves $1/2$ $E_{\text{max}}$; $g$ represents the residual variance function by study; and $\varepsilon$ 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 $E_{\text{max}}$ 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 $E_{\text{max}}$ model with parameters (maximum drug effect: $E_{\text{max}}$; dose producing 50% of the maximum effect: $E_{50}$ (measure of potency); placebo response: $P_0$) 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 $C_{\text{max}}$, $C_{\text{min}}$, and $C_{eq}$ for efficacy endpoints. To characterize the most relevant tofacitinib PK parameter for efficacy and assess the predictive value of $C_{\text{max}}$ over and above $C_{eq}$, efficacy data at Week 12 from four phase II studies were analyzed. Steady-state subject-specific PK parameters ($C_{eq}$, $C_{\text{max}}$, and $C_{\text{min}}$) were predicted from a population PK model in RA patients.\(^{41}\) For DAS28, a standard $E_{\text{max}}$ 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, $C_{\text{min}}$ was added to the E-R model as a covariate of $E_{\text{max}}$ or $EC_{50}$ to a model having $C_{eq}$ as the predictor, to evaluate if $C_{\text{min}}$ had any added predictive value over and above $C_{eq}$. In Stage 3, a sensitivity analysis was conducted by reversing the order of the testing, whereby $C_{\text{min}}$ was set as the predictor and $C_{eq}$ was included as a covariate on $E_{\text{max}}$ or $EC_{50}$. The general form of the equation for Stages 2 and 3 is shown below:

$$D=\theta_D \cdot (1+\theta_P (P=\text{median}(P)))$$

where $D$ is the drug-effect parameter $\theta_D$ ($E_{\text{max}}$ or $EC_{50}$); $\theta_P$ is the fractional change in $D$; $P$ is the PK parameter ($C_{eq}$ or $C_{\text{min}}$). 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 ($\Delta$ 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.

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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. 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. 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. analyzed the data.

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