Model-Based Comparison of Dose-Response Profiles of Tofacitinib in Japanese Versus Western Rheumatoid Arthritis Patients

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Abstract
Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis (RA). The aim of this analysis was to characterize the relationship between tofacitinib dose and efficacy, as measured by American College of Rheumatology (ACR) response rates, and to compare this between Japanese and Western patients with RA. Efficacy data were pooled from 2 double-blind, dose-ranging phase 2 studies of tofacitinib monotherapy 1-15 mg twice daily in patients with RA with an inadequate response to disease-modifying antirheumatic drugs (DMARDs). NCT00550446 was carried out in mostly Western patients and NCT00687193 in Japanese patients. ACR20, ACR50, and ACR70 response rates in week 12 were analyzed using maximum drug effect (Emax) models on the logit domain. Both studies showed a dose-response for each end point, supporting the efficacy of tofacitinib in patients with inadequate response to DMARDs. Study-specific differences in Emax were noted, whereas potency (dose providing half the maximum effect [ED50]) was similar across studies. After adjustment for study differences in Emax by calculating the fractions of the maximum placebo-adjusted proportion of ACR responses, the estimated locations for the 5- and 10-mg twice-daily doses on the dose-response curves were similar for the 2 patient populations: ACR20, ACR50, and ACR70 mean fractional responses for 5 and 10 mg twice daily were 0.78, 0.43, 0.32 and 0.90, 0.69, and 0.56, respectively, for the Japanese study and 0.54, 0.41, and 0.22 and 0.73, 0.61, and 0.40, respectively, for the Western study. This analysis therefore supports the rationale for the same dosing regimen in Japanese patients as in Western patients from an efficacy perspective.

Keywords
dose-response, Japanese, rheumatoid arthritis, tofacitinib, efficacy

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). Tofacitinib is a potent selective inhibitor of the JAK family of kinases with approximately 1000-fold selectivity over 82 other kinases tested in the selectivity panel compared with the potency of JAK3 (1 nM).¹⁻³ In cellular settings in which JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1, with functional selectivity over receptors that signal via pairs of JAK2.²,⁴ Inhibition of JAK1/3 by tofacitinib is proposed to block signaling through the common gamma chain containing receptors for several cytokines, including interleukin (IL)-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, proliferation, and function, and inhibition of their signaling may result in suppression of multiple aspects of the immune response.⁵ In addition, crossover to JAK1 may result in some attenuation of signaling by additional cytokines such as IL-6 and interferon-γ.⁴

The efficacy and safety of tofacitinib 5 and 10 mg twice daily administered as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), mainly methotrexate, in patients with moderately to severely active RA, have been demonstrated in phase 2,⁶⁻¹⁰ phase 3,¹¹⁻¹⁶ and phase 3b/⁴¹⁷ studies of up to 24 months’ duration and in long-term extension studies with up to 9.5 years’ observation.¹⁸⁻²⁰

In Japan, the currently approved tofacitinib dosing regimen is 5 mg twice daily administered as monotherapy or in combination with csDMARDs for the treatment of patients with RA who have an inadequate response to at least 1 csDMARD or biologic DMARD.²¹ It has been previously demonstrated that ethnic or racial differences in different patient populations (eg, differences in genetic makeup, renal or hepatic function, or body weight) can affect a drug’s pharmacokinetic (PK) profile, leading to variability in efficacy and safety profiles.²² The objectives of this analysis were to

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compare the dose-response profiles in RA for Western patients with those of Japanese patients using a model-based comparison approach to evaluate similarities and differences in the maximum drug effect ($E_{\text{max}}$) model parameters. Study NCT00550446$^6$ was a phase 2 study in mostly Western patients with active RA and an inadequate response to ≥1 DMARD (hereafter referred to as the Western study), which compared 5 dosing regimens of tofacitinib monotherapy and adalimumab 40 mg every other week versus placebo, administered for 6 months. Study NCT00687193$^10$ was a dose-finding phase 2 study of tofacitinib monotherapy conducted in Japanese patients with active RA and an inadequate response to ≥1 DMARD (hereafter referred to as the Japanese study).

The American College of Rheumatology (ACR) criteria were used to calculate 20%, 50%, and 70% improvements in RA (ACR20, ACR50, and ACR70, respectively).$^{23}$ Assessment of the similarities between the predicted dose-ACR20, dose-ACR50, and dose-ACR70 response profiles in Japanese and Western patients with RA could inform selection of “equivalent” doses in Japanese patients relative to Western patients. Previously the PK parameters of tofacitinib were shown to be similar in the 2 populations.$^{24,25}$ In this analysis, pooled ACR20, ACR50, and ACR70 response rates in week 12 from the Western study and the Japanese study were used to support $E_{\text{max}}$ model parameter estimation. Dose-response data have been modeled based on other clinical trials for tofacitinib.$^{26,27}$ This is the first dose-response analysis for the Japanese study.

**Methods**

Both these multicenter studies were approved by the institutional review boards/independent ethics committees for each study center. All patients provided written informed consent.$^6,10$

Comparison of the similarities and differences between the dose-response profiles for Western patients and Japanese patients with RA were assessed using a model-based approach.

**Study Design**

The Western study was a phase 2B randomized, double-blind, placebo-controlled, active comparator, multicenter 6-month trial that compared 5 dosing regimens of tofacitinib, and adalimumab, both administered as monotherapy with placebo and was conducted in mostly Western patients with active RA who failed an adequate trial of therapy with at least 1 DMARD because of lack of efficacy or toxicity. A total of 555 patients were screened; 386 were randomized to study treatment, and 384 received study drug or placebo. Patients were randomized in a 1:1:1:1:1:1:1 ratio to receive 1 of 5 active doses of tofacitinib (1, 3, 5, 10, or 15 mg twice daily), placebo, or adalimumab 40-mg subcutaneous injections every other week.$^6$

The Japanese study was a phase 2 randomized, double-blind, placebo-controlled, multicenter 12-week trial conducted to establish the dose-ACR20 response profile of tofacitinib administered as monotherapy. The target sample size was 300 Japanese patients with RA (50 patients per group) who had an inadequate response to ≥1 DMARD because of lack of efficacy or toxicity or a change in drugs because of safety reasons. A total of 383 patients were screened; 318 were randomized to study treatment, and 317 received study drug or placebo. Patients were randomized in a 1:1:1:1:1:1 ratio to 1 of 5 active doses of tofacitinib (1, 3, 5, 10, or 15 mg twice daily) or placebo.$^{10}$

**Study Assessments**

Efficacy measurements were assessed at baseline and in weeks 2, 4, 6, 8, 10, 12, 16, 20, and 24, including early termination, for the Western study. For the Japanese study, the same measurements were assessed at baseline and in week 2, 4, 8, and 12, including early termination.

ACR20, ACR50, and ACR70 were defined as 20%, 50%, or 70% improvement, respectively, from baseline in tender/painful joints (68 joint count), swollen joints (66 joint count), and at least 3 of 5 ACR core set measures: Patient’s Global Assessment of Arthritis Pain (VAS), disability (as measured by Health Assessment Questionnaire-Disability Index [HAQ-DI]), or an acute-phase reactant (C-reactive protein concentrations).$^{23}$

The following parameters were assessed for the Disease Activity Score (DAS) assessment using erythrocyte sedimentation rate (ESR; DAS28-4[ESR]): tender/painful joint count (assessed in 28 joints), swollen joint count (assessed in 28 joints), ESR, Patient’s Global Assessment of Arthritis.

**Data for Analysis**

Data from 2 clinical studies were pooled. ACR response rates in week 12 were used as a measure of efficacy dose-response in the current analysis, as this was the last point common to both studies. Pharmacodynamic steady state was expected by week 12.$^{27}$ Baseline values for DAS and HAQ-DI were evaluated as possible covariates affecting the ACR response rate. Data from the adalimumab group in the Western study were excluded from the analysis because the objective of this analysis was to evaluate the dose-response profile of tofacitinib monotherapy. The last observation carried forward method was used to impute missing ACR component.
data prior to modeling, which was in accordance with the imputation method used for the primary end-point analysis for both the Western and the Japanese studies.

There were 17 patients with missing values for baseline DAS28-4(ESR) and 2 patients with missing values for baseline HAQ-DI scores in the Western study. Patients with missing values for either baseline DAS28-4(ESR) or HAQ-DI scores were excluded from evaluation of DAS28-4(ESR) or HAQ-DI scores as covariates, respectively.

Other covariates that were used to evaluate the similarity in Japanese and non-Japanese populations in the analysis were effect of study (Western or Japanese study), sex, race (Asian or non-Asian), and body weight. The effect of the covariates on the 3 parameters of the Emax model (Emax, half the maximum effect [ED50], and E0) were examined for each parameter individually and in combination.

Software and Strategy
The analysis was performed using generalized non-linear modeling methodology as implemented in the NONMEM software system, version 6, level 2.0 (GloboMax LLC, Hanover, Maryland) and the NM-TRAN subroutines version III, level 1.2, and the PREDPP model library, version V, level 1.0, using Intel-based PC Workstations running Red Hat Linux (3.4.6-8) operating systems and GNU Fortran compilers (GCC 3.4.6 20060404) using optimization level “-O.”

The analysis was performed to estimate the population parameters and identify potential covariates affecting the parameters. Maximum likelihood estimation was used to estimate the model parameters to evaluate whether the Japanese and Western dose-ACR response profiles were similar in week 12. No Japanese patients were enrolled in the Western study, and no non-Japanese patients were enrolled in the Japanese study. Therefore, study was used as a race designation of Japanese or Western, and all other race covariates applied only to the Western study. Some non-Japanese Asians were enrolled in the Western study; therefore, the effect of Asian/non-Asian was evaluated in an attempt to investigate the effect of race distinct to study effect.

Base Model Description
A simple Emax model on the logit domain was fitted to the dose-response data as shown below:

\[
\log \Pr(ACR_i = 1) = E_0 + \frac{E_{\text{max}} \cdot D_i}{D_i + E_{D50}}
\]

where \(P(ACR_i = 1)\) denotes the probability for positive ACR response (ACR20, ACR50, or ACR70 in subject i); \(D_i\) is the randomized dose (in milligrams) for each administration given twice-daily for subject i; \(E_0\) is the logit of the placebo response (\(D_i = 0\)); \(E_{\text{max}}\) is the maximum drug effect, that is, the contribution to the logit at very large \(D_i\); and \(E_{D50}\) is the dose that yields a tofacitinib effect of \(\frac{1}{2}\) \(E_{\text{max}}\).

The estimated parameter for \(E_{D50}\) was exponentiated within the model equation to constrain the value in the expression to a positive value (ie, \(\log E_{D50}\) was estimated). The same model was fitted to ACR20, ACR50, and ACR70 data in the current study analysis. To calculate 90% predictive intervals, data for 1000 trials, based on study design and population from the Japanese and Western studies, were generated using NONMEM-derived maximum likelihood parameter estimates.

Inclusion of Covariates
Effects of study, race (Asian or non-Asian), body weight, baseline DAS-28(ESR), and baseline HAQ-DI on the 3 parameters of the Emax model, that is, \(E_{\text{max}},\ E_{D50},\) and \(E_0\), were examined for each parameter individually and in combination.

For \(E_{\text{max}}\) and \(E_{D50}\), the effect of a dichotomous covariate \(x\) (study or race) was modeled as multiplicative effects of the form:

\[
\theta = \theta_0 \cdot (\theta_x)^x
\]

where \(\theta_0\) denotes the population value of the parameter for the null value of the covariate \(x\) (ie, \(x = 0\)); \(\theta\) denotes the population value conditional on the value of \(x\), which is a function of the power parameter \(\theta_x\); \(\theta_x\) denotes the fractional change in \(\theta_0\) when \(x = 1\) (ie, \(x = 1\) for effect of the Japanese study compared with the Western study, or \(x = 1\) for effect of Asian race compared with non-Asians).

Continuous covariates (body weight, baseline DAS28-4[ESR] score, or baseline HAQ-DI score) were modeled as multiplicative effects of the form:

\[
\theta = \theta_0 \cdot (x/x_{\text{norm}})^{\theta_x}
\]

where \(x_{\text{norm}}\) denotes the reference value of \(x\) for centering the estimate (eg, the average weight in the data set was used as the \(x_{\text{norm}}\) for weight); \(\theta_0\) denotes the population value of the parameter when \(x = x_{\text{norm}}\); \(\theta\) denotes the population value conditional on the value of \(x\), which is a function of the power parameter \(\theta_x\).

When \(\theta_x = 1\), \(\theta\) is proportional to \(x/x_{\text{norm}}\). The term for “\(x/x_{\text{norm}}\)” was exponentiated for the assessment of baseline HAQ-DI scores to keep the value to a nonzero value.

For \(E_0\), the effect of a dichotomous covariate \(x\) (study or race) was modeled as additive effects of the form:

\[
\theta = \theta_0 + (\theta_x) \cdot x
\]

where \(\theta_0\) denotes the population value of the parameter for the null value of the covariate \(x\) (ie, \(x = 0\)); \(\theta\) denotes the population value conditional on the value of \(x\),
which is a multiplicative function to parameter $\theta_x$; $\theta_x$ denotes an additive change in $\theta_0$ when $x = 1$.

Continuous covariates (body weight) were modeled as additive effects of the form effects:

$$
\theta = \theta_0 + (x - x_{norm}) \cdot \theta_x
$$

where $\theta_0$ denotes the population value of the parameter when $x = x_{norm}$ (e.g., $x_{norm} = 63$ kg for weight); $\theta$ denotes the population value conditional on the value of $x$, which is a multiplicative function to parameter $\theta_x$.

**Final Model Development**

Covariate inclusion was evaluated in a univariate manner and was based on changes in objective function values. Covariate effects were added to 1 of the 3 parameters of the $E_{\text{max}}$ model, that is, $E_{\text{max}}$, $E_{50}$, and $E_0$, and/or another one of the remaining parameters, depending on the drop in objective function. The final model was selected according to the drop in objective function values.

**Assessment of Model Predictive Performance**

The predictive performance of the final model was evaluated using a visual predictive check. Ninety percent prediction intervals were constructed for the model predictions as a function of dose, and the observed ACR response rates were compared with these intervals. In addition, prediction intervals for $\Delta(D)$, where $\Delta(D)$ is the estimate for the difference in predicted ACR response rates between the Western study and the Japanese study as a function of dose, were computed and compared with the data-based estimates to evaluate the appropriateness of the model-based assessment of similarity.

**Comparison of Dose-Response Profiles Between Japanese and Western Patients**

The focus of the analysis was to evaluate whether Japanese and Western ACR response rates were similar as a function of dose. The 90% confidence intervals (CIs) for the final model were calculated to make this evaluation. In addition to comparing parameter estimates and standard errors of the model parameters between the 2 studies, a comparison of the shapes of the dose-response curves for ACR20, ACR50, and ACR70 was also performed after adjusting for differences in $E_{\text{max}}$. The motivation for applying such an approach was based on the assumption that maximum drug effect is more likely to be influenced by a combination of factors such as drug effect, disease state, design, inclusion/exclusion criteria, and so forth, whereas $E_{50}$ may be more reflective of the intrinsic potency of the compound.

The fraction of the maximum placebo-adjusted proportion of ACR responses for a particular study was calculated using NONMEM-derived maximum likelihood estimates in the following equations:

$$
p(D_i) = \frac{\exp(E_0 + E_{\text{max}} \cdot D_i/(D_i + E_{50}))}{1 + \exp(E_0 + E_{\text{max}} \cdot D_i/(D_i + E_{50}))}
$$

$$
p(\text{placebo}) = \frac{\exp(E_0)}{1 + \exp(E_0)}
$$

$$
p(\text{max}) = \frac{\exp(E_0 + E_{\text{max}})}{1 + \exp(E_0 + E_{\text{max}})}
$$

$$
Fr(\text{max change}) = \frac{p(D_i) - p(\text{placebo})}{p(\text{max}) - p(\text{placebo})}
$$

where $p(D_i)$ is the probability of positive ACR response for dose $D_i$; $p(\text{placebo})$ is the probability of positive ACR response for placebo; $p(\text{max})$ is the model-based maximum probability of positive ACR response, $D_i$; and $E_0$, $E_{\text{max}}$, and $E_{50}$ are as previously defined.

Model-based predictive check intervals were obtained by simulating the number of responders for dose $D$, placebo, and maximum effect on the assumption of binomial distribution, for multiple trials.

**Results**

**Observed Data**

Table 1 shows the summary of demographic data and the baseline disease status as assessed by

|                         | The Japanese Study, $n = 317$ | The Western Study, $n = 331$ | Total, $n = 648$ |
|-------------------------|-------------------------------|-------------------------------|------------------|
| **Female, %**           | 83.3                          | 87.0                          | 85.2             |
| **Race, %**             |                               |                               |                  |
| **White**               | 0                             | 75.8                          | 38.7             |
| **Black**               | 0                             | 2.4                           | 1.2              |
| **Asian**               | 100                           | 9.4                           | 32.2             |
| **Other**               | 0                             | 12.4                          | 6.3              |
| **Age (years), mean (SD)** | 53.4 (11.2)                  | 53.3 (12.7)                  | 53.4 (12.0)      |
| **Range**               | 20-70                         | 18-83                         | 18-83            |
| **Weight (kg), mean (SD)** | 54.4 (9.8)                   | 70.3 (16.5)                  | 62.5 (15.8)      |
| **Range**               | 31.4-85.6                     | 41.0-125                      | 31.4-125         |
| **Height (cm), mean (SD)** | 157 (7)                      | 161 (9)                      | 159 (8)          |
| **Range**               | 140-177                       | 131-198                       | 131-198          |
| **DAS28-4(ESR), mean (SD)** | 6.1 (1.0)                  | 6.5 (0.9)                     | 6.3 (1.0)        |
| **Range**               | 3.2-8.8                       | 3.4-8.6                       | 3.2-8.8          |
| **HAQ-DI, mean (SD)**   | 1.3 (0.7)                     | 1.5 (0.7)                     | 1.4 (0.7)        |
| **Range**               | 0.0-2.9                       | 0.0-3.0                       | 0.0-3.0          |

DAS28-4(ESR), disease activity score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; SD, standard deviation.

Patients with missing values for either DAS28-4(ESR) or HAQ-DI scores were excluded.
DAS28-4(ESR) and HAQ-DI scores in the Japanese and Western studies. The percentage of female patients enrolled and average age were similar in both studies. Patients enrolled in the Japanese study had a smaller body weight compared with those in the Western study. In the Japanese study, all patients were Japanese, whereas in the Western study, most of the patients were white, none were Japanese, and 31 of a total of 331 were Asian. The baseline DAS28-4(ESR) and baseline HAQ-DI scores were slightly lower for the Japanese study than for the Western study.

**Base Model Results**

The base E\textsubscript{max} model (no covariates) was fitted to the pooled data for the Japanese and Western studies. As shown in Figure 1, the observed responder rates were well within the 90% predictive intervals with no evidence of bias as a function of dose, suggesting that the model adequately describes the data. However, when observed data were plotted by study, although generally within the predictive interval, the observed data seemed to fall within the upper half of the predictive interval for the Japanese study or the lower half of the predictive interval for the Western study. This suggests some differences in ACR20, ACR50, and ACR70 response profiles between the 2 studies.

**Final Model Results**

Table 2 shows the changes in minimum value of objective function (MOF) values when the study effect was examined as a covariate on each of the 3 parameters of the E\textsubscript{max} model independently.

The drop in the objective function value was largest when study effect was included in E\textsubscript{max} ($P < .01$, $df = 1$). When study effect was included on ED\textsubscript{S0} or E\textsubscript{0} in addition to E\textsubscript{max}, the objective function value drop was smaller than would have been expected from the results when study effect was included in E\textsubscript{max}, ED\textsubscript{S0}, or E\textsubscript{0} independently. The inclusion of study effect on ED\textsubscript{S0} alone showed nearly as large a drop in the objective function as when study effect was included in E\textsubscript{max} alone. The data set did not allow differentiation between the parameters in terms of covariate effects.

Trial differences between differing study populations are confounded because of the demographics of patients enrolled in the Japanese study and the Western study. However, as there were some Asian patients enrolled in the Western study, the effect of race (Asian or non-Asian) and body weight on each of the 3 parameters of the E\textsubscript{max} model was examined in an attempt to evaluate the study effect. With respect to race, the drop in the objective function value was largest when race effect was included in E\textsubscript{max} (ACR20, ACR50, and ACR70, -9.6, -7.8, and -18.1, compared with -8.8, -5.8, and -16.6 and -3.7, -4.1, and -13.4 when race effect was added on ED\textsubscript{S0} and E\textsubscript{0}, respectively; Supplementary Table S1). When body weight was examined as a covariate on each of the 3 parameters of the E\textsubscript{max} model independently, the drop in the objective function was not statistically significant (significance level of $\alpha = 0.01$, $df = 1$; Supplementary Table S2).

The inclusion of baseline DAS28-4(ESR) or HAQ-DI values caused very little, if any, decrease in the ΔMOF, suggesting that there are no obvious differences in ACR response according to baseline disease state as assessed by DAS28-4(ESR) (ACR20, ACR50, ACR70, -1.0, -0.44, -0.23; -0.48, -0.01, -0.11; and -2.5, -0.45, -0.42 when baseline DAS28-4[ESR] was added on E\textsubscript{max}, ED\textsubscript{S0}, and E\textsubscript{0}, respectively; Supplementary Table S3) and HAQ-DI (ACR20, ACR50, ACR70, -0.42, -0.04, -0.01; -0.26, -0.17, and -0.38 when HAQ-DI was added on E\textsubscript{max}, ED\textsubscript{S0}, and E\textsubscript{0}, respectively; Supplementary Table S4). These observations are in agreement with overall demographic data from the data set, which showed only slight differences in baseline values for DAS28-4(ESR) and HAQ-DI between the 2 studies (Table 1). The slight drop in objective function value was in agreement with results from stratification of model-based dose-response curves by baseline DAS28-4(ESR) or HAQ-DI, which did not reveal any difference in dose-response between the quartiles (data not shown). Likewise, raw data plots for body weight and ACR responses by dose revealed no difference in the range of baseline DAS28-4(ESR) or HAQ-DI between responders and nonresponders (data not shown).

**Parameter Estimate Results**

Table 3 shows the parameter estimates for the base model for ACR responses when E\textsubscript{max} models were fitted to the Japanese study or the Western study independently or to pooled data from the 2 studies.

When the base model was fitted to the 2 studies independently, the estimated E\textsubscript{max} was approximately 40%-70% greater in the Japanese study than in the Western study. Table 4 shows the parameter estimates for the final model for ACR responses. The drop in the objective function value was largest when study effect was included in E\textsubscript{max} ($P < .01$, $df = 1$). The parameter estimate for study effect on E\textsubscript{max} was 1.4, 1.3, and 1.5 for ACR20, ACR50, and ACR70, respectively, indicating an approximately 30%-50% greater E\textsubscript{max} in the Japanese study compared with the Western study. This was consistent with the differences in E\textsubscript{max} when the base model was fitted to the 2 studies independently. When study effect was included in ED\textsubscript{S0} or E\textsubscript{0} in addition to E\textsubscript{max}, the objective function value drop was smaller than would have been expected from the results when study effect was included in E\textsubscript{max},
Figure 1. Mean (90%CI) model-predicted ACR20, ACR50, and ACR70 responses in week 12 for the base model. Shaded range shows 90% prediction interval (from 5.0 to 95.0 percentile points) of simulation based on binomial distribution. To calculate 90% predictive intervals, data for 1000 trials, based on study design and population from the Japanese and Western studies, were generated using NONMEM-derived maximum likelihood parameter estimates. Parameter estimates to depict the predictive intervals were derived from pooled data. ACR, American College of Rheumatology response criteria.
Table 2. Results for Study Effect

| Description | Run No. | MOF  | ΔMOF |
|-------------|---------|------|------|
| Base model  | 1       | 742.4| -    |
| Add effect on E_{max} | 2       | 723.2| -10.2 (from base) |
| Add effect on ED_{50} | 3       | 733.5| -8.9 (from base) |
| Add effect on E_{0}    | 4       | 738.3| -7.1 (from base) |
| Add effect on E_{max} and ED_{50} | 5       | 715.2| 0.0 (from run 2) |
| Add effect on E_{max} and E_{0} | 6       | 710.4| -6.3 (from run 2) |

ACR50

| Description | Run No. | MOF  | ΔMOF |
|-------------|---------|------|------|
| Base model  | 1       | 718.3| -    |
| Add effect on E_{max} | 2       | 710.5| -7.8 (from base) |
| Add effect on ED_{50} | 3       | 712.6| -5.7 (from base) |
| Add effect on E_{0}       | 4       | 714.5| -3.8 (from base) |
| Add effect on E_{max} and ED_{50} | 5       | 709.5| -0.96 (from run 2) |
| Add effect on E_{max} and E_{0} | 6       | 708.8| -1.7 (from run 2) |

ACR70

| Description | Run No. | MOF  | ΔMOF |
|-------------|---------|------|------|
| Base model  | 1       | 571.6| -    |
| Add effect on E_{max} | 2       | 555.9| -15.8 (from base) |
| Add effect on ED_{50} | 3       | 557.1| -14.6 (from base) |
| Add effect on E_{0}       | 4       | 560.2| -11.4 (from base) |
| Add effect on E_{max} and ED_{50} | 5       | 555.7| -0.1 (from run 2) |
| Add effect on E_{max} and E_{0} | 6       | 555.6| -0.87 (from run 2) |

ACR, American College of Rheumatology response criteria; E_{0}, logit of the placebo response; E_{max}, maximum drug effect; ED_{50}, dose that yields an effect of E_{max}/2; MOF, minimum value of objective function; ΔMOF, change in MOF.

Final Model Predictive Performance

A visual predictive check was performed by comparing the 90% prediction intervals for the model predictions as a function of dose with the observed ACR response rates. As shown in Figure 2, the inclusion of study effect on ED_{50} alone showed nearly as large a drop in the objective function as when study effect was included in E_{max} alone. There was no additional information when adding a study effect on ED_{50} in addition to study effect on E_{max}, and the final model results suggest that inclusion of study effect on E_{max} adjusts the model, thus making it more useful and fit for the situation.

Comparison of Dose-Effect Profile Between Japanese and Non-Japanese Patients

As shown in Figure 3, the fraction of the maximum, placebo-adjusted proportion of ACR responders in ED_{50}, or E_{0} independently. However, the inclusion of study effect on ED_{50} alone showed nearly as large a drop in the objective function as when study effect was included in E_{max} alone. There was no additional information when adding a study effect on ED_{50} in addition to study effect on E_{max}, and the final model results suggest that inclusion of study effect on E_{max} adjusts the model, thus making it more useful and fit for the situation.

Final Model Predictive Performance

A visual predictive check was performed by comparing the 90% prediction intervals for the model predictions as a function of dose with the observed ACR response rates. As shown in Figure 2, the inclusion of study effect on E_{max} explained the differences in the observed data for the Japanese study and the Western study. The observed responder rates were well within the prediction intervals when plotted for the pooled data, the Japanese study data, or the Western study data, suggesting that the model adequately describes the data.

Comparison of Dose-Effect Profile Between Japanese and Non-Japanese Patients

As shown in Figure 3, the fraction of the maximum, placebo-adjusted proportion of ACR responders in

week 12 was calculated to explore differences in the potency of tofacitinib in the Japanese study and the Western study after accounting for the differences in E_{max}. The mean (90%CI) fractional ACR responses for 5 and 10 mg twice daily are shown in Table 5.
Figure 2. Mean (90% CI) model-predicted ACR20, ACR50, and ACR70 responses in week 12 for the final model with study effect on E_{max}. Shaded range shows 90% prediction interval (from 5.0 to 95.0 percentile points) of simulation based on binomial distribution. To calculate 90% prediction, data for 1000 trials, based on study design and population from the Japanese and Western studies, were generated using NONMEM-derived maximum likelihood parameter estimates. Parameter estimates to depict the predictive intervals were derived from pooled data. ACR, American College of Rheumatology response criteria; CI, confidence interval; E_{max}, maximum drug effect.
Figure 3. Mean fraction of the maximum, placebo-adjusted proportion of ACR20, ACR50, and ACR70 responders in week 12. Lines show median and 90% prediction interval (from 5 to 95 percentile points) of simulation based on binomial distribution. To calculate 90% prediction intervals, data for 1000 trials, based on study design and population from the Japanese and Western studies, were generated using NONMEM-derived maximum likelihood parameter estimates. ACR, American College of Rheumatology response criteria.

Table 5. Fraction of the Maximum, Placebo-Adjusted Proportion of ACR Responders in Week 12 for 5 and 10 mg Twice Daily

| Response | Dose a | Mean (90%CIb) Fractional Response |
|----------|--------|----------------------------------|
|          |        | The Japanese Study | The Western Study |
| ACR20    | 5 mg   | 0.78 (0.63-0.91)    | 0.54 (0.31-0.75) |
|          | 10 mg  | 0.90 (0.78-1.02)    | 0.73 (0.56-0.91) |
| ACR50    | 5 mg   | 0.43 (0.29-0.57)    | 0.41 (0.21-0.63) |
|          | 10 mg  | 0.69 (0.55-0.83)    | 0.61 (0.42-0.82) |
| ACR70    | 5 mg   | 0.32 (0.18-0.47)    | 0.22 (0.01-0.46) |
|          | 10 mg  | 0.56 (0.40-0.73)    | 0.40 (0.17-0.65) |

ACR, American College of Rheumatology response criteria; CI, confidence interval.

aShown as dose for each dose given.
b90%CI derived from simulation of 1000 trials.

Although the wide CIs imply considerable uncertainty around the estimates, the fractions of maximum effect for 5- and 10-mg twice-daily doses were essentially similar in the Japanese study and the Western study for ACR50 and ACR70, whereas ACR20 rates appeared to show some differences, especially for 5 mg. These findings are generally consistent with ED50 estimates in the base model, suggesting possible differences for ACR20, but not for ACR50 and ACR70 response rates between the 2 studies.

Discussion

The objective of this analysis was to evaluate dose-response relationships of tofacitinib in Japanese and Western patients with RA for ACR20, ACR50, and ACR70 responses to inform selection of “equivalent” doses in Japanese patients relative to Western patients.

Application of an Emax model showed that the Emax estimates were higher by 30%-50% in the Japanese study than in the Western study. This was not an unexpected finding because clinical trials have revealed higher response rates to some biologic agents (including infliximab, etanercept, and tocilizumab) in patients with RA in Japan than in patients receiving the same treatments in Western countries.28 Therefore, it was not clear whether the higher Emax estimate implied that lowering the dose of tofacitinib would produce equivalent responses in Japanese and Western patients with RA. To better understand the data, the ACR20, ACR50, and ACR70 dose-response relationships were further compared based on ED50 estimates and by calculating fractions of the maximum placebo-adjusted proportions, that is, after adjusting for differences in Emax. This was done based on the principle that maximum drug effect may be more likely to be influenced by a combination of intrinsic and extrinsic factors, such as drug effect, disease state, design, inclusion/exclusion criteria environmental and medical backgrounds, and so forth, whereas ED50 may be more reflective of the intrinsic property of the molecule.

These results indicate that the mean (90%CI) fractions of the maximum placebo-adjusted proportions, particularly for ACR50 and ACR70, were similar in the Japanese and Western studies, with overlapping
Conclusions

Based on current data, dose-response profiles for tofacitinib could be modeled adequately with an E\textsubscript{max} model, with study effect on E\textsubscript{max} as an influential covariate on the dose-response.

After adjustment for study differences in E\textsubscript{max} by calculating the fractions of maximum placebo-adjusted proportion of ACR responses, the estimated locations for the 5- and 10-mg twice-daily doses on the dose-response curves were similar for the Japanese and Western studies, supporting the rationale for the same dosing regimen in Western and Japanese patients.

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Conflicts of Interest

M. Suzuki, S. Shoji, S. Miyoshi, and S. Krishnaswami are employees of and hold stocks and shares in Pfizer Inc.

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Data-Sharing Statement

On request and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or the European Union, or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions and for whom an exception does not apply via a secure portal. To gain access, data requesters must enter into a data-access agreement with Pfizer.

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