Bridging Efficacy of Tofacitinib Immediate-Release to Extended-Release Formulations for Treatment of Ulcerative Colitis: Application of a Model-Informed Drug Development Approach

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Abstract

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). We report a model-informed drug development approach for bridging efficacy from immediate-release (IR) to extended-release (XR) tofacitinib formulations in patients with UC. IR-XR efficacy bridging was supported by exposure-response analysis of phase 3 induction/maintenance studies of the IR formulation in UC to identify exposure metrics relevant for efficacy. Pharmacokinetic studies in healthy subjects were used to confirm similarity of relevant exposure metrics of tofacitinib IR 5 mg twice daily to XR 11 mg once daily, and tofacitinib IR 10 mg twice daily to XR 22 mg once daily, thereby bridging efficacy between IR and XR formulations. Food effect was evaluated at both XR formulation dose levels. Exposure-response analysis demonstrated that area under the plasma concentration–time curve (average plasma concentration) was a relevant predictor of efficacy. Pharmacokinetic studies demonstrated that area under the plasma concentration–time curve was equivalent between formulations under single-dose and steady-state conditions, and other exposure metrics were also similar. These results also supported bridging of safety data for IR-XR formulations. Food had no impact on tofacitinib XR exposure. These data support efficacy/safety bridging of IR-XR formulations in patients with UC.

Tofacitinib is an oral, small molecule Janus kinase inhibitor for the treatment of ulcerative colitis (UC). The efficacy and safety of tofacitinib has been established in patients with moderately to severely active UC in an 8-week phase 2 induction study (NCT00787202),[1] two 8-week phase 3 induction studies (OCTAVE Induction 1 and 2; NCT01465763, NCT01458951),[2] a 52-week phase 3 maintenance study (OCTAVE Sustain; NCT01458574),[2] and a phase 3, multicenter, open-label, long-term extension study (OCTAVE Open; NCT01470612).[3]

While tofacitinib is available as an immediate-release (IR), twice daily formulation,[4] for chronic conditions that require long-term maintenance treatment, such as UC, a once daily dosing option may be more convenient and could optimize ease of use and compliance.[5] An extended-release (XR) formulation of tofacitinib

was developed to provide a once daily equivalent to the tofacitinib IR twice daily formulation, with tofacitinib XR 11 and 22 mg once daily equivalent to tofacitinib IR 5 and 10 mg twice daily, respectively

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(the 10% increase in total daily dose of tofacitinib was necessary to match the area under the plasma concentration–time curve [AUC] of the IR formulation).[6]

Previous investigations in healthy volunteers found that tofacitinib was absorbed rapidly, plasma concentrations peak ≈1.0 hours after oral administration, and mean half-life ($t_{1/2}$) was ≈3 hours.[7,8] The majority of tofacitinib clearance (70%) was via hepatic metabolism, while only 30% of tofacitinib clearance was due to renal elimination.[7,8] Tofacitinib was mainly metabolized by cytochrome P450 (CYP) 3A4 (53%), with a smaller contribution from CYP2C19 (17%).[7,8] In addition, the pharmacokinetics (PK) of other drugs (including those metabolized by CYP450 isoenzymes or eliminated by the kidney) were not significantly altered by tofacitinib. However, inhibitors or inducers of CYP450 may alter exposure to tofacitinib.[9]

Approval of the tofacitinib XR 11 and 22 mg once daily formulations in the United States[4] was based on a model-informed drug development approach, with XR formulation development informed by a series of biopharmaceutical studies in healthy volunteers.[6] Results from these studies demonstrated equivalence of AUC and maximum plasma concentration (C_{max}) of tofacitinib XR 11 mg once daily compared with tofacitinib IR 5 mg twice daily.[6] Also, AUC was shown to be the relevant parameter for prediction of efficacy in patients with rheumatoid arthritis (RA) using exposure-response (E-R) evaluations of randomized controlled trials of the IR formulation.[9] Based on these results, efficacy of the tofacitinib XR 11 mg once daily formulation was successfully bridged from the tofacitinib IR 5 mg twice daily formulation in patients with RA.[9] The same bridging strategy used in RA was applied to bridge tofacitinib XR 11 mg once daily and XR 22 mg once daily in UC.

Here, we report the results of a post hoc E-R analysis of the relationship between PK parameters (also referred to as exposure metrics) and efficacy in patients with moderately to severely active UC in the tofacitinib OCTAVE program. The purpose of the E-R analysis was to identify the exposure metric most relevant for efficacy in patients with UC. The bridging of efficacy from IR to XR formulations was supported by the similarity of the relevant exposure metric between the IR and XR formulations in phase 1 studies in healthy volunteers. The approach was similar to that previously used to bridge efficacy between the tofacitinib XR and IR formulations in patients with RA.[9] Additionally, to support this bridging analysis, we also report the results of 2 phase 1 studies that evaluated the PK and safety of tofacitinib XR 22 mg once daily in healthy volunteers: first, a relative bioavailability (rBA) study that investigated the PK and safety of tofacitinib XR 22 mg once daily relative to tofacitinib IR 10 mg twice daily under single-dose and steady-state dosing conditions; and second, a food-effect (FE) study that investigated the effect of food on the PK and safety of tofacitinib XR 22 mg.

Methods

OCTAVE UC Phase 2 and 3 Study Designs

The post hoc E-R analysis included data from patients enrolled in the 8-week phase 2 induction study (NCT00787202),[1] two 8-week phase 3 induction studies (OCTAVE Induction 1 and 2),[2] and the 52-week phase 3 maintenance study (OCTAVE Sustain).[2] Details of the study designs have been reported previously.[1,2] Briefly, in the phase 2 induction study, patients with moderately to severely active UC were randomized to receive either tofacitinib IR 0.5, 3, 10, or 15 mg twice daily or placebo. In OCTAVE Induction 1 and 2, patients with UC were randomized to receive either tofacitinib IR 10 mg twice daily or placebo. In OCTAVE Sustain, patients who completed OCTAVE Induction 1 or 2 with a clinical response at week 8 (defined as a decrease from baseline Mayo score of ≥3 points and ≥30%, plus a decrease in rectal bleeding subscore of ≥1 or rectal bleeding subscore ≤1) were rerandomized to receive tofacitinib 5 or 10 mg twice daily or placebo.

The phase 2 induction study was conducted at 51 centers in 17 countries; OCTAVE Induction 1 and 2 were conducted at 144 sites and 169 sites worldwide, respectively; and OCTAVE Sustain was conducted at 297 sites worldwide (Table S1). All study protocols were approved by each center's institutional review board or independent ethics committee, and written informed consent was obtained from all participants before study initiation. Studies were conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines. Additional information regarding independent ethics committees and institutional review boards is reported in Table S2.

OCTAVE UC Phase 2 and 3 Studies: Blood Sampling for PK Analysis and PK Parameters

Full details regarding blood sampling for PK analysis in the OCTAVE clinical program have been previously reported.[10] Tofacitinib concentrations were analyzed at WuXi AppTec (Shanghai, China) using a previously validated analytical method,[11] which was updated for this current analysis. Assay precision and accuracy were within acceptable ranges in all studies (Table S3).

In the post hoc E-R analysis, the average plasma concentration (C_{avg}; directly proportional to the AUC), C_{max}, the minimum plasma concentration (C_{min}), and the duration of time (over a 24-hour dosing interval

at steady state) when the exposure was above the IC_{50} (the exposure at which 50% of maximum inhibition is observed [$TAIC_{50}$]) were evaluated as predictors of efficacy. Additional information regarding estimation of these metrics is reported in the Supplemental Information.

### OCTAVE UC Phase 2 and 3 Studies: Logistic Regression E-R Analysis

The relationships between the PK parameters (C_{avg}, C_{max}, C_{min}, and $TAIC_{50}$) and efficacy end points (remission and endoscopic improvement) were described using a logistic regression model at week 8 of the 3 induction studies (phase 2 Induction and OCTAVE Induction 1 and 2), and at weeks 24 and 52 of the maintenance study (OCTAVE Sustain). Logistic regression analysis with either linear or maximum drug effect models of E-R was used to test each PK parameter as a predictor of efficacy end points. The models that were applied to the analysis of remission and endoscopic improvement are summarized in Table 2 and Table S4, respectively. Comparisons of model fit were based on changes in objective function values (OFVs), Akaike information criterion, and evaluation of diagnostic plots.

Phase 1 Studies

Healthy volunteers were enrolled in 2 separate phase 1, randomized, open-label, 2-period, 2-way crossover studies: an rBA study and an FE study (NCT02487433).

The 2-week rBA study investigated the equivalence of the PK and the safety of single and steady-state dosing with tofacitinib XR 22 mg once daily versus tofacitinib IR 10 mg twice daily. Healthy volunteers were randomized 1:1 to 1 of 2 treatment sequences and underwent an overnight fast of at least 10 hours before receiving tofacitinib; each treatment sequence was then further subdivided into 2 treatment periods. In rBA sequence 1, period 1, volunteers received a single dose of tofacitinib XR 22 mg on day 1 (single dose), followed by a washout of at least 48 hours before receiving tofacitinib XR 22 mg once daily on days 3 to 6 (steady-state dosing). In rBA sequence 2, period 1, volunteers received tofacitinib IR 10 mg twice daily ≈12 hours apart on day 1 (therefore, total dose administered was 20 mg, defined as "single dose") followed by IR 10 mg twice daily on days 3 to 6 (steady-state dosing). At the end of period 1 (day 6 in both treatment sequences), there was washout of at least 72 hours, after which volunteers crossed over to treatment period 2. Volunteers in rBA sequence 1, period 2 then received single-dose tofacitinib IR (ie, tofacitinib IR 10 mg twice daily) on day 1 of period 2, followed by steady-state dosing with tofacitinib IR 10 mg twice daily on days 3 to 6 of period 2. Volunteers in rBA sequence 2, period 2
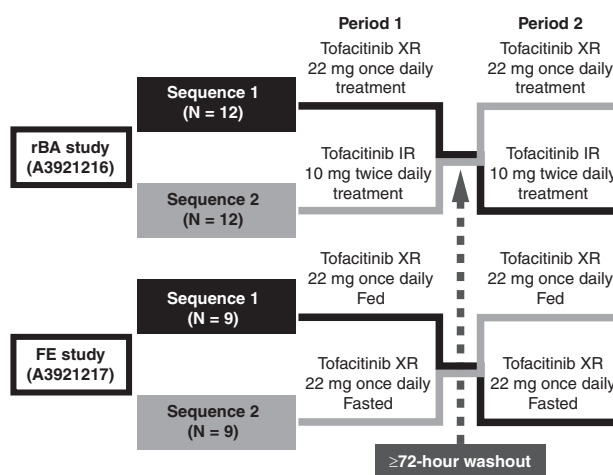
Figure 1. Study treatment sequences of the rBA and FE studies. FE, food effect; IR, immediate-release; rBA, relative bioavailability; XR, extended-release.

then received single-dose tofacitinib XR 22 mg on day 1 of period 2, followed by steady-state dosing with tofacitinib XR 22 mg once daily on days 3 to 6 of period 2 (Figure 1).

The 1-week FE study investigated the effect of food on the PK and safety of single doses of tofacitinib XR 22 mg. Healthy volunteers were randomly assigned 1:1 to receive tofacitinib XR 22 mg once daily in 2 treatment sequences, which were further subdivided into 2 treatment periods. In FE sequence 1, period 1, participants underwent a 10-hour fast, followed by a standard US Food and Drug Administration–approved, high-fat, high-calorie breakfast (described in full in the Supplemental Methods); tofacitinib was administered within 30 minutes of feeding. In FE sequence 2, period 1, participants received tofacitinib after a 10-hour fast. At the end of period 1, volunteers underwent a washout of at least 72 hours before crossing over to the next treatment period, where participants in FE sequence 1, period 2 received tofacitinib after a 10-hour fast, and participants in FE sequence 2, period 2 received tofacitinib under fed conditions (Figure 1).

All study protocols were approved by the institutional review board or independent ethics committee for each center, and written informed consent was obtained from all participants (or their guardian/s) before study initiation. Studies were conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation Good Clinical Practice Guidelines. Additional information regarding independent ethics committees and institutional review boards is reported in Table S5. Both phase 1 studies took place at a single center in Belgium (Table S5).

Phase 1 Studies: Blood Sampling for PK Analysis and PK Parameters

Full details regarding blood sampling for PK analysis in the rBA and FE studies are reported in the Supplemental Information. In both the rBA and FE studies, PK parameters were calculated by standard noncompartmental methods. In the rBA study, PK parameters were determined for both the XR and IR administration periods. In the rBA study, mean (standard deviation) plasma tofacitinib concentration–time profiles were calculated for tofacitinib XR 22 mg once daily and tofacitinib IR 10 mg twice daily after single-dose administration on day 1 and steady-state dosing on day 6; values that were below the limit of quantitation were considered to be 0 in calculation of means. Bioequivalence was demonstrated for single-dose and steady-state dosing if the 90%CI for the adjusted geometric mean ratio (XR/IR) for the AUC from time 0 extrapolated to infinite time (AUC_{inf}) and the AUC from time 0 to 24 hours (AUC_{24}), respectively, fell wholly within equivalence limits (80%-125%). In the FE study, mean (standard deviation) plasma tofacitinib concentration–time profiles were calculated for tofacitinib XR 22 mg once daily in fed and fasted conditions; values below the limit of quantitation were considered to be 0 in calculation of means. Bioequivalence was demonstrated if the 90%CI for the fed/fasted ratio for AUC_{inf} fell wholly within equivalence limits (80%-125%). See the Supplemental Information for full details.

Phase 1 Studies: Safety

In the rBA and FE studies, all adverse events (AEs) were reported, regardless of treatment or suspected causal relationship to the study drug.

Results

OCTAVE UC Phase 2 and 3 Studies: Patient Demographics and Characteristics

In total, 1355 patients from the UC induction studies and 592 patients from the UC maintenance study were analyzed in the post hoc E-R analysis. The majority of patients were male (induction, n = 786; maintenance, n = 329) and White (induction, n = 1105; maintenance, n = 472). In the induction and maintenance studies, respectively, the mean age was 41.3 years and 42.8 years, mean weight was 73.4 and 74.8 kg, and mean body mass index (BMI) was 24.9 and 25.5 kg/m^2 (Table 1).

OCTAVE UC Phase 2 and 3 Studies: Logistic Regression Analysis

Correlations between PK parameters in the post hoc E-R analysis are shown in Table S6.

In the Phase 2 induction study in the post hoc E-R analysis, all PK parameters provided similar model fits for both clinical remission and endoscopic

Table 1. Demographics and Characteristics of Patients With UC Analyzed in the Post Hoc E-R Analysis

	Induction Studies (N = 1355)	Maintenance Study (N = 592)
Male, n (%)	786 (58.0)	329 (55.6)
Age, y, mean (SD)	41.3 (13.9)	42.8 (14.0)
[range]	[18-81]	[18-80]
Race, n (%)[a]		
White	1105 (81.5)	472 (79.7)
Black	13 (1.0)	5 (0.8)
Asian	145 (10.7)	74 (12.5)
Other	56 (4.1)	23 (3.9)
Weight, kg, mean (SD)	73.4 (16.6)	74.8 (16.6)
[range]	[37.0-154.5]	[31.3-155.0]
BMI, kg/m^2, mean (SD)	24.9 (4.9)	25.5 (4.9)
[range]	[10.6-54.6]	[11.8-55.6]
Height, cm, mean (SD)	172.0 (9.6)	171.0 (9.6)
[range]	[143.0-199.0]	[146.0-199.0]

BMI, body mass index; E-R, exposure-response; N, number of evaluable patients in each study; n, number of patients with characteristic; SD, standard deviation; UC, ulcerative colitis; y, years.
Information on race was unavailable for 36 patients in the induction studies and 18 patients in the maintenance study.

improvement (Table 2 and Table S4). There were no significant differences in OFV when PK parameters were evaluated individually. This finding was consistent with similar model fits across different PK parameters, as demonstrated in diagnostic plots (Figure 2A and Figure S1A).

In OCTAVE Induction 1 and 2, C_{avg} and C_{max} had very similar model performances for remission. However, the OFV for the C_{avg} model was >3.8 points lower than the OFV for the C_{min} and $TAIC_{50}$ models, indicating a better model fit with C_{avg} (Table 2). For endoscopic improvement, model performance for C_{avg} was similar to C_{max} and $TAIC_{50}$ and was better than that of C_{min} (Table S4). The model diagnostic plots across PK parameters indicated overall similar model fits (Figure 2B and Figure S1B).

In OCTAVE Sustain, OFVs were lower for C_{min} and $TAIC_{50}$ than for C_{avg} and C_{max}, for remission and endoscopic improvement. C_{min} was a slightly better model fit than $TAIC_{50}$ for endoscopic improvement (ΔOFV = 4.5; Table S4). The model diagnostic plots across PK parameters (Figure 2C and Figure S1C) indicated overall similar model fits.

Given the demonstrated similarity of all exposure metrics between the IR and XR formulations, the safety profile of the XR formulation was expected to be similar to, or better than, that of the IR formulation in patients with UC. Therefore, further E-R analyses of safety end points in patients with UC were not required to support bridging of safety data between formulations.
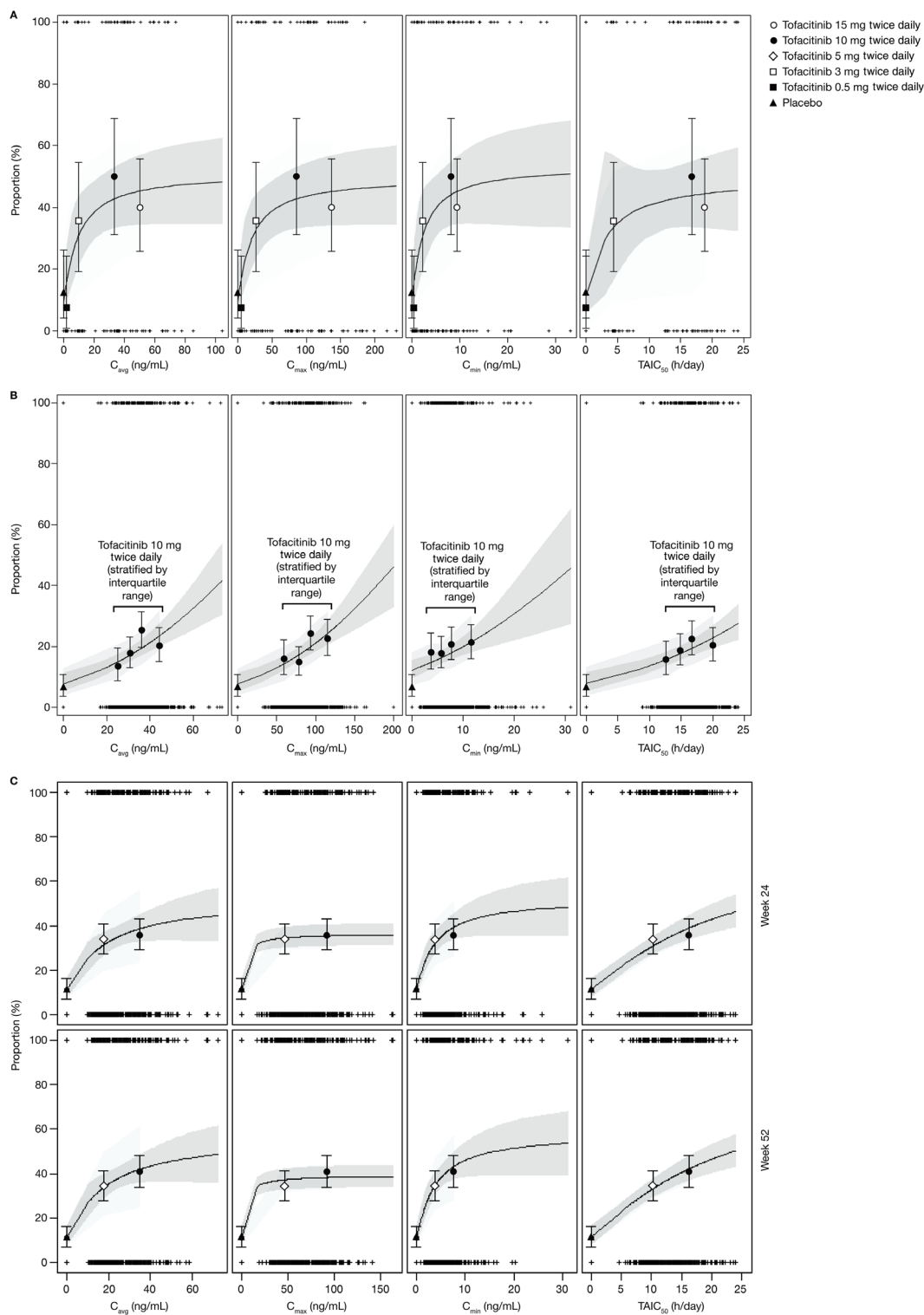
Figure 2. Observed and model-predicted proportions of patients in remission in (A) phase 2 induction study, (B) OCTAVE Induction 1 and 2, and (C) OCTAVE Sustain. Results were based on linear logistic E_{max} models. Symbols and error bars represent observed proportions and 95%CIs binned by quartiles of each exposure metric (plotted at the midpoint of each bin), and solid line and shaded region represent model-predicted probabilities and 95%CIs (dark gray shaded) and 95%PIs (light gray shaded). CIs and PIs in C_{max} and $TAIC_{50}$ models were obtained from models where EC_{50} was fixed to its point estimate. Individual values of each exposure metric are shown by symbols (+) along the *x*-axis at *y*-axis values of 0% (nonresponders) or 100% (responders). C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; EC_{50}, exposure at which 50% of maximum drug effect is observed; E_{max}, maximum drug effect; IC_{50}, exposure at which 50% of maximum inhibition is observed; PI, prediction interval; $TAIC_{50}$, duration of time (over a 24-hour dosing interval at steady-state) when the exposure is above the IC_{50}.

Table 2. Summary of E-R Models for Remission[a] in the OCTAVE Clinical Program

	E-R Model	Primary PK Parameter	OFV (AIC[b]) First Stage	Comments
Phase 2 Induction	1	C_{avg}	190.6	Relative to model 4, OFV 0.9 points higher, indicating similar model fit
	2	C_{max}	191.3	Relative to model 4, OFV 1.6 points higher, indicating similar model fit
	3	C_{min}	190.6	Relative to model 4, OFV 0.9 points higher, indicating similar model fit
	4	$TAIC_{50}$	189.7	Model with lowest OFV
OCTAVE Induction 1 and 2	1	C_{avg}	951.7	Relative to model 2, OFV 0.7 points higher, indicating similar model fit to C_{max} model
	2	C_{max}	951.0	Model with lowest OFV
	3	C_{min}	967.9	Relative to model 2, OFV 16.9 points higher, indicating better model fit to C_{max} model
	4	$TAIC_{50}$	955.6	Relative to model 2, OFV 4.6 points higher, indicating better model fit to C_{max} model
OCTAVE Sustain	1	C_{avg}	1301.8	Relative to model 3, OFV 5.3 points higher, indicating better model fit to C_{min} model
	2	C_{max}	1306.8	Relative to model 3, OFV 10.3 points higher, indicating better model fit to C_{min} model
	3	C_{min}	1296.5	Model with lowest OFV
	4	$TAIC_{50}$	1300.1	Relative to model 3, OFV 3.6 points higher, indicating similar model fit to C_{min} model

$\triangle$OFV, difference in OFV between reduced and full model; AIC, Akaike information criterion; C_{avg}, average plasma concentration; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; E-R, exposure-response; IC_{50}, exposure at which 50% of maximum inhibition is observed; OFV, objective function value (-2LogLikelihood); PK, pharmacokinetics; $TAIC_{50}$, duration of time (over a 24-hour dosing interval at steady-state) when the exposure is above IC_{50}; χ^2, chi-square.
Significance was assessed by comparing $\triangle$OFV against a χ^2 distribution with one degree of freedom (χ^2 value was 3.84; equivalent to a *P* value of .05).
[a] Clinical remission in the phase 2 trial.
[b] AIC = OFV + 2Np, where Np means number of parameters (Np = 2 for first stage, Np = 3 for second stage).

Phase 1 Studies: Healthy Volunteer Demographics and Characteristics

In the rBA study, 24 healthy volunteers were randomized to treatment (rBA sequence 1, n = 12; rBA sequence 2, n = 12), completed the study, and contributed samples for PK analysis. All volunteers were male and the majority were White (n = 21). The mean age was 30.2 years, mean weight was 77.5 kg, and mean BMI was 24.1 kg/m^2 (Table 3).

In the FE study, 18 healthy volunteers were randomly assigned to treatment (FE sequence 1, n = 9; FE sequence 2, n = 9), completed the study, and contributed samples for PK analysis. All volunteers were male and the majority were White (n = 12). The mean age was 32.3 years, mean weight was 77.8 kg, and mean BMI was 24.5 kg/m^2 (Table 3).

Phase 1 Studies: PK Parameters

In the rBA study, following single-dose administration on day 1, the XR/IR (90%CI) ratio was 98.3% (94.3-102.4) for AUC_{inf} and 87.9% (78.1-98.9) for C_{max} (Table 4). Median time to C_{max} (t_{max}) was longer for tofacitinib XR 22 mg once daily (3.0 hours

Table 3. Volunteer Demographic and Characteristics of Volunteers From the rBA and FE Studies

	rBA Study (N = 24)	FE Study (N = 18)
Male, n (%)	24 (100.0)	18 (100.0)
Age, y, mean (SD)	30.2 (8.8)	32.3 (9.3)
[range]	[19-47]	[19-46]
Race, n (%)		
White	21 (87.5)	12 (66.7)
Black	3 (12.5)	3 (16.7)
Asian	0 (0.0)	3 (16.7)
Weight, kg, mean (SD)	77.5 (13.5)	77.8 (14.1)
[range]	[55.2-106.6]	[59.0-102.2]
BMI, kg/m^2, mean (SD)	24.1 (3.3)	24.5 (3.7)
[range]	[18.0-29.6]	[17.8-30.3]
Height, cm, mean (SD)	179.1 (8.5)	178.1 (6.7)
[range]	[161-193]	[166-190]

BMI, body mass index; FE, food effect; N, number of evaluable healthy volunteers in each study; n, number of healthy volunteers with characteristic; rBA, relative bioavailability; SD, standard deviation; y, years.

[range, 2.0-4.0 hours]) than tofacitinib IR 10 mg twice daily (0.5 hours [range, 0.5-13.0 hours]; Table 4). Mean (arithmetic) $t_{1/2}$ was also longer for tofacitinib

Table 4. Summary of Plasma Tofacitinib PK Parameter Values Following Administration of Tofacitinib XR 22 mg Once Daily or IR 10 mg Twice Daily in the rBA Study

	Tofacitinib XR 22 mg Once Daily	Tofacitinib IR 10 mg Twice Daily	Ratio (90%CI)[a]
Single-dose analysis (day 1)			
AUC_{inf}, ng • h/mL			
Geometric mean (geometric %CV)	527.6 (27)	536.7 (23)	98.3 (94.3-102.4)
Arithmetic mean (SD)	545.0 (134.5)	550.5 (125.9)	NA
AUC_{24}, ng • h/mL			
Geometric mean (geometric %CV)	497.1 (27)	516.1 (22)	NA
Arithmetic mean (SD)	513.3 (125.7)	527.5 (112.5)	NA
C_{max}, ng/mL			
Geometric mean (geometric %CV)	71.9 (29)	81.9 (20)	87.9 (78.1-98.9)
Arithmetic mean (SD)	74.8 (21.6)	83.3 (15.5)	NA
t_{max}, h, median (range)	3.0 (2.0-4.0)	0.5 (0.5-13.0)	NA
$t_{1/2}$, h, arithmetic mean (SD)	7.7 (3.46)	3.9 (0.96)	NA
Steady-state analysis (day 6)			
AUC_{24}, ng • h/mL			
Geometric mean (geometric %CV)	596.6 (19)	539.6 (22)	110.6 (105.5-115.9)
Arithmetic mean (SD)	606.9 (112.2)	551.8 (121.1)	NA
C_{max}, ng/mL			
Geometric mean (geometric %CV)	83.8 (25)	83.6 (19)	100.2 (90.5-110.8)
Arithmetic mean (SD)	86.3 (21.5)	85.0 (15.1)	NA
C_{min}, ng/mL			
Geometric mean (geometric %CV)	3.1 (43)	3.2 (54)	97.5 (84.0-113.2)
Arithmetic mean (SD)	3.4 (1.3)	3.6 (1.7)	NA
t_{max}, h, median (range)	4.0 (2.0-4.0)	0.8 (0.5-14.0)	NA

AUC, area under the plasma concentration–time curve; AUC_{inf}, AUC from time 0 extrapolated to infinite time; AUC_{24}, AUC from time 0 to 24 h; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; IR, immediate-release; NA, not applicable; PK, pharmacokinetics; rBA, relative bioavailability; SD, standard deviation; $t_{1/2}$, half-life; t_{max}, time to C_{max}; XR, extended-release; %CV, percent coefficient of variation.
[a] Ratios and 90%CIs are expressed as percentages.

XR 22 mg once daily (7.7 hours) compared with tofacitinib IR 10 mg twice daily (3.9 hours; Table 4). The plasma concentration–time profiles are shown in Figure 3.

Following steady-state dosing on day 6, the XR/IR (90%CI) ratio was 110.6% (105.5-115.9) for AUC_{24}, 100.2% (90.5-110.8) for C_{max}, and 97.5% (84.0-113.2) for C_{min} (Table 4). Median t_{max} was longer for tofacitinib XR 22 mg once daily (4.0 hours [range, 2.0-4.0 hours]) than for tofacitinib IR 10 mg twice daily (0.8 hours [range, 0.5-14.0 hours]; Table 4).

In the FE study, the fed/fasted (90% CI) ratio was 104.9% (98.1-112.0) for AUC_{inf} (Table 5). Mean (geometric) C_{max} was higher under fed conditions (78.6 ng/mL) than under fasted conditions (66.2 ng/mL), and was reached 0.5 hours later (median t_{max} was 4.0 hours and 3.5 hours for the fed and fasted groups, respectively; Table 5). Mean (arithmetic) $t_{1/2}$ was shorter under fed conditions (5.3 hours) than under fasted conditions (6.9 hours; Table 5). The plasma concentration–time profiles are shown in Figure 4.

Phase 1 Studies: Safety
In the rBA study, a total of 21 treatment-emergent AEs were reported in 12 healthy volunteers. No serious AEs, severe AEs, discontinuations or dose reduction due to AEs, or deaths were reported. Approximately 11 (52.4%) treatment-emergent AEs were considered to be treatment-related by the investigator. Safety results from the FE study are reported in the Supplemental Information.

Discussion
Results from the post hoc E-R analysis of patients with UC found generally consistent results for efficacy endpoints (remission and endoscopic improvement) in the phase 2 induction study, OCTAVE Induction 1 and 2, and OCTAVE Sustain. In OCTAVE Induction 1 and 2, C_{avg} and C_{max} were the best predictors of remission, and C_{avg}, C_{max}, and $TAIC_{50}$ were the best predictors of endoscopic improvement. In OCTAVE Sustain, $TAIC_{50}$ and C_{min} were the best predictors of remission, whereas C_{min} provided the best predictor for endoscopic improvement. Overall, predictive properties for all PK
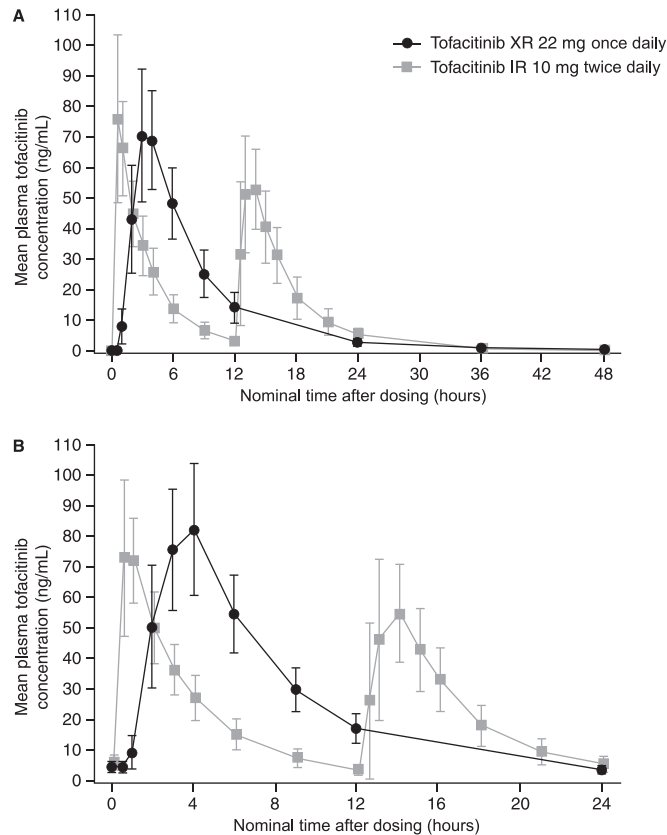
Figure 3. Mean (SD) plasma tofacitinib concentration–time profiles in the rBA study for tofacitinib XR 22 mg once daily and tofacitinib IR 10 mg twice daily after (A) single-dose administration on day 1 and (B) steady-state dosing on day 6. BLQ values were considered to be 0 in calculation of means. BLQ, below the limit of quantitation; IR, immediate-release; rBA, relative bioavailability; SD, standard deviation; XR, extended-release.

Table 5. Summary of Plasma Tofacitinib PK Parameter Values Following Administration of Tofacitinib XR 22 mg Under Fed and Fasted Conditions in the FE Study

| FE Study	Fed (N = 18)	Fasted (N = 18)	Ratio (90%CI)[a]
AUC$_{inf}$, ng • h/mL			
Geometric mean (geometric %CV)	514.5 (23)	490.7 (18)	104.9 (98.1-112.0)
Arithmetic mean (SD)	527.9 (126.1)	498.1 (87.5)	NA
C$_{max}$, ng/mL			
Geometric mean (geometric %CV)	78.6 (35)	66.2 (26)	118.7 (101.6-138.6)
Arithmetic mean (SD)	83.2 (31.6)	68.2 (16.9)	NA
t$_{max}$, h, median (range)	4.0 (3.0-9.0)	3.5 (3.0-4.1)	NA
t$_{1/2}$, h, arithmetic mean (SD)	5.3 (2.00)	6.9 (2.7)	NA

AUC, area under the plasma concentration–time curve; AUC$_{inf}$, AUC from time 0 extrapolated to infinite time; C$_{max}$, maximum plasma concentration; FE, food effect; NA, not applicable; PK, pharmacokinetics; SD, standard deviation; t$_{1/2}$, half-life; t$_{max}$, time to C$_{max}$; XR, extended-release; %CV, percent coefficient of variation.
[a] Ratios and 90%CI are expressed as percentages.

parameters were generally similar, and the analysis did not conclusively identify one parameter over another as the most important for clinical efficacy in patients with UC, likely due to the high correlation among these predictors. C$_{avg}$ and TAIC$_{50}$, which are metrics of overall exposure, were included among the best predictors in each analysis, identifying them as relevant and sufficient predictors of efficacy in UC induction and maintenance studies. Additionally, since all 4 PK parameters (C$_{avg}$, C$_{max}$, C$_{min}$, and TAIC$_{50}$) were similar between the IR and XR formulations, these analyses support the bridging of efficacy from the IR to the XR formulation.
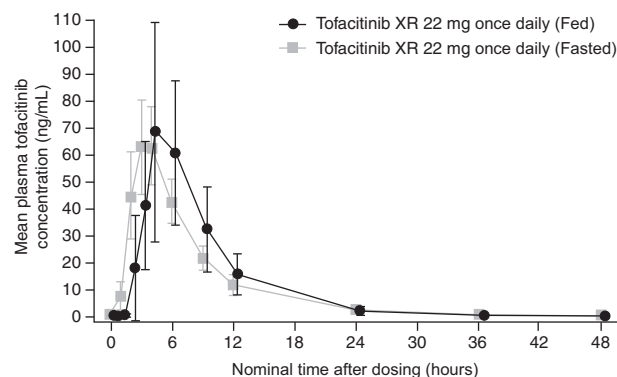
Figure 4. Mean (SD) plasma tofacitinib concentration–time profiles in the FE study for tofacitinib XR 22 mg once daily in fed and fasted conditions. BLQ values were considered to be 0 in calculation of means. BLQ, below the limit of quantitation; FE, food effect; IR, immediate-release; SD, standard deviation; XR, extended-release.

The phase 1 studies reported here assessed the PK and safety of tofacitinib XR 22 mg once daily relative to tofacitinib IR 10 mg twice daily under single-dose and steady-state conditions, as well as the effect of food on the PK of tofacitinib XR 22 mg once daily, to further support the evidence for E-R bridging efficacy and the use of tofacitinib XR formulations in patients with UC. The results of the rBA study support the bioequivalence of tofacitinib XR 22 mg once daily and tofacitinib IR 10 mg twice daily both following single-dose administration on day 1 and under steady-state conditions on day 6. Specifically, based on 90% CI for the XR/IR ratio of adjusted geometric means within the 80% to 125% interval, bioequivalence was demonstrated for AUC_{inf} following single-dose administration on day 1, and for AUC_{24}, under steady-state conditions on day 6. As might be expected, t_{max} and $t_{1/2}$ were longer with the XR formulation.

These results were consistent with the previously reported results of 2 phase 1 studies of tofacitinib XR 11 mg once daily in healthy volunteers, the first of which compared the PK of tofacitinib XR 11 mg once daily and tofacitinib IR 5 mg twice daily under single-dose and steady-state conditions (Pfizer study A3921212).[6] Consistent with the results of the rBA study reported here, bioequivalence was demonstrated between tofacitinib XR once daily and tofacitinib IR twice daily for AUC_{inf} under single-dose conditions.[6] C_{max} was similar with both formulations (adjusted geometric mean, 38.2 ng/mL with tofacitinib XR 11 mg once daily and 40.9 ng/mL with tofacitinib IR 5 mg twice daily; C_{max} ratio, 93.4% [90%CI, 84.1-103.7]). Additionally, t_{max} in this previous study was reached later with tofacitinib XR 11 mg once daily (4.0 hours) than with tofacitinib IR 5 mg twice daily (0.5 hours); the same pattern was noted with $t_{1/2}$ (5.9 and 3.2 hours, respectively). As discussed in this previous study, the

discrepancy in $t_{1/2}$ between the XR and IR formulations is likely to be because of the absorption-limited disposition of tofacitinib due to extended drug release.[6] Consistent with the results of the rBA study reported here, bioequivalence between tofacitinib XR once daily and tofacitinib IR twice daily was demonstrated for AUC_{24} under steady-state conditions.

The FE study data support the bioequivalence of tofacitinib XR 22 mg once daily under fed and fasted conditions for the AUC parameter. These results were also consistent with the previously reported phase 1 study (NCT02084875), in which C_{max} and t_{max} were higher and $t_{1/2}$ was shorter under fed vs fasted conditions, but overall exposure was demonstrated to be bioequivalent. Overall, the results from the E-R analysis reported here, which found that all PK parameters were generally similar as predictors of efficacy, along with previous E-R analyses in RA indicating that C_{avg} was the most relevant predictor of efficacy,[9] suggested that the difference in C_{max} between fed and fasted states in the FE study was unlikely to be clinically relevant. Tofacitinib was generally well tolerated in healthy volunteers participating in the phase 1 studies reported here when administered as XR 22 mg once daily or IR 10 mg twice daily, and under fed or fasted conditions.

There was no notable difference in the incidence of AEs observed between treatments in the phase 1 studies. Safety results for both studies were consistent with those reported previously in phase 1 studies that demonstrated bioequivalence between tofacitinib XR 11 mg once daily and tofacitinib IR 5 mg twice daily under single-dose and steady-state conditions.[6] These findings align with previous findings that the incidence of AEs was similar for XR and IR formulations.[4] In addition, as PK parameters were found to be bioequivalent between the IR and XR formulations, this provides evidence of safety bridging.

Efficacy bridging between tofacitinib XR 11 mg once daily and IR 5 mg twice daily has been previously demonstrated in patients with RA.[9] The applicability of E-R evidence in RA to the bridging of efficacy of XR to IR at both dose levels in patients with UC was supported by the consistency of PK and E-R relationships between the 2 indications. The E-R relationships in RA and UC were informed by efficacy data obtained over a wide range of IR twice daily doses, ranging from tofacitinib 1 mg twice daily to 15 mg twice daily in RA,[9] and from tofacitinib 0.5 mg twice daily to 15 mg twice daily in UC, supporting the applicability of the bridging approach across dose levels. Comparison of E-R analyses of week 8 induction efficacy data in UC to E-R analyses of week 12 efficacy data in RA has indicated similar overall E-R characteristics.[9]

Use of tofacitinib XR delivery allows a similar extent of in vivo drug absorption from single-dose

administration as can be achieved by the twice daily IR formulation. Compared with healthy individuals, longer colonic transit times and increased colon permeability due to colonic lesions have been reported in patients with UC.[12–14] This longer transit time in UC could potentially impact on how PK data in healthy volunteers translate to the UC setting, and also impact the applicability of XR-IR bridging efficacy previously achieved in the RA population to the UC population. However, previous in vitro dissolution studies with tofacitinib 11 and 22 mg XR have indicated that ≈80% of tofacitinib administered in the XR formulation was absorbed within 6 hours in the small intestine, prior to arrival in the colon.[15] In addition, small intestine median transit times in healthy individuals and patients with severe UC were reported as 4.9 and 5.9 hours, respectively[13]; therefore, only a small fraction of the XR dose is potentially subject to UC disease-specific effects and, consequently, there is no reason to expect a difference in absorption of XR formulations in patients with UC vs healthy individuals. In addition, any increase in exposure is expected to be <10%, which is not likely to be clinically relevant for safety, given the present low rates of important safety events of interest with the IR formulation.[16] The available data in healthy volunteers, along with these considerations, provide assurance of an overall similar exposure between IR and XR in patients with UC.

A limitation of this post hoc analysis was that the data were from clinical trials that were not designed to evaluate efficacy bridging of IR and XR formulations of tofacitinib. Another limitation of this analysis was that it used data from controlled populations of a small number of healthy volunteers enrolled in phase 1 studies, which may not necessarily be representative of the real-world population with UC.

In conclusion, results from the post hoc E-R analysis and phase 1 clinical studies provide supportive evidence that the tofacitinib XR formulations offers similar PK, efficacy, and safety profiles to the IR formulation in patients with UC.

Acknowledgments

Conflicts of Interest

Author Contributions

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Supplemental Information

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