CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208246Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	208246
Submission Date	4/24/2015
Brand Name	XELJANZ XR
Generic Name	Tofacitinib MR
Clinical Pharmacology Reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacometrics Reviewer	Jianmeng Chen, M.D., Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Team Leader	Ping Ji, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Pfizer, Inc.
Submission Type; Code	505(b)(1); standard review
Formulation; Strength(s)	MR Tablet 11 mg
Indication	Rheumatoid Arthritis
Dosage Regimen	11 mg QD

---

1. Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology finds NDA 208246 acceptable.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

1.3.1 Background

This application seeks approval for the tofacitinib modified release (MR) 11 mg once daily (QD) tablet formulation for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate. The proposed MR Formulation provides a QD dosing alternative to Xeljanz®, the currently approved tofacitinib immediate release (IR) tablet formulation (NDA203214, approved Nov 6, 2012) administered 5 mg twice daily (BID).

Sponsor supported this NDA submission with 7 phase 1 studies, and additional exposure-response analysis to support bridging of efficacy and safety based on PK equivalence.

1.3.2 Pharmacokinetics (PK)

PK summary: Tofacitinib MR vs. IR

Table 1. Summary of PK parameters for tofacitinib IR and MR

Tofacitinib	**IR**	**MR (osmotic tablet)**
Bioavailability	74%	10% less relative to IR
T_{max}	<1h	3-4h
$T_{1/2}$	3h	5-6h
Linear PK	yes	yes
Food effect	No	No (C_{max}↑ 20%, AUC↔)
Accumulation	No	No

(Source: Reviewer summary)

Across the pilot and other phase 1 studies, the geometric mean C_{max} and AUC_{inf} ranged from 36.10- 42.20 ng/mL and 253-314 ng.hr/mL, respectively under fasting conditions for the proposed commercial MR 11 mg (extrudable core system [ECS] osmotic) tablet formulation. The median T_{max} and mean t½ values ranged from 3.00-4.00 hours and 5.45-6.25 hours, respectively. In the single and multiple-dose PK study (A3921212), multiple dose to single dose accumulation ratios were approximately 1.06 and 1.12 for C_{max} and AUC, respectively for the MR formulation, indicating negligible accumulation following repeat dosing of the tofacitinib MR formulation. Trough (pre-dose) concentration monitoring indicates that steady state concentrations are achieved within 48 hours of repeat dosing of MR 11 mg QD.

Exposure Comparison: Tofacitinib MR vs. IR

Evaluation of relative BA for the MR 11 mg formulation compared to the IR 5 mg formulation has demonstrated equivalence of AUC and C_{max} in pivotal PK study A3921212 (Table 2), as well as other studies. At steady state, C_{min} for MR 11 mg QD is approximately 29% lower and C_{trough} is approximately 26% lower compared to IR 5 mg BID (Table 2).

Table 2. Summary of PK of Tofacitinib MR 11mg QD compared to Tofacitinib IR 5mg BID (study A3921212)

Parameter (Unit)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a] (%)	90% CI for Ratio
	MR 11 mg QD (Test)	IR 5 mg BID (Reference)		
Day 1 (Single Dose Phase)				
AUC_{inf} (ng•hr/mL)	253.2	243.7	103.92	98.81, 109.28
C_{max} (ng/mL)	35.98	39.22	91.75	83.27, 101.09
Day 5 (Multiple Dose Phase)				
AUC_{24} (ng•hr/mL)	268.5	263.4	101.94	97.79, 106.27
C_{max} (ng/mL)	38.19	40.89	93.41	84.14, 103.69
C_{min} (ng/mL)	1.044	1.478	70.64	59.01, 84.56
C_{trough} (ng/mL)	1.820	2.475	73.54	57.71, 93.70

a. The ratios (and 90% CIs) are expressed as percentages.

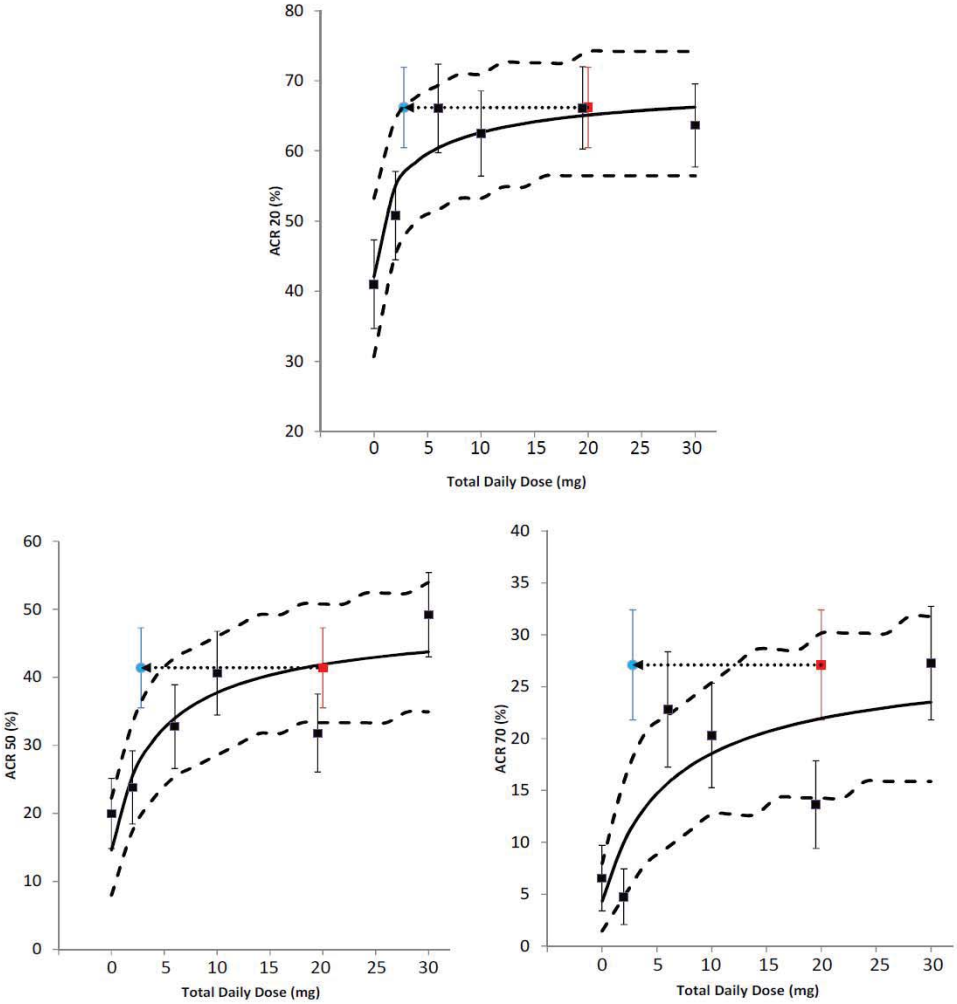
AUC_{inf} = Area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{24} = Area under the plasma concentration-time profile from time zero to 24 hours; C_{max} = maximum plasma concentration; C_{min} = Minimum plasma concentration; C_{trough} = Predose plasma concentration; CI = Confidence Interval; IR= Immediate Release; MR = Modified Release.

(Source: Table 13 and Table 15, study A3921212 CSR)

1.3.3 Exposure-Response Relationship

- **Efficacy**: The observed data and application of PK/PD modeling approaches consistently showed that C_{av} appears the most relevant parameter for efficacy and that the 29% lower C_{min} for the MR formulation may not be clinically important to the efficacy of tofacitinib. Similar clinical efficacy was observed with IR 20 mg QD dose compared to IR 10 mg BID despite a large difference in C_{min} (Figure 1), and the

improved goodness of fit characteristics with C_{av} compared to C_{max} or C_{min} suggested C_{av} as the most relevant PK parameter for efficacy.



The observed proportion of ACR20/50/70 responders for IR 20 mg QD dose at Week 12 is overlaid with model-predicted posterior mean (10^{th}-90^{th} percentiles) from a longitudinal E_{max} model applied to BID doses in Study A3921025. Doses are presented on a total daily dose scale.
Black solid line represents posterior mean model prediction, black dashed line represents 80% prediction intervals from the model; black filled squares represent observed data for BID doses; red filled square and blue filled circle represent 20 mg QD data placed either at a x-axis value of 20 (reflecting the same AUC_{24} as 10 mg BID) or at a x-axis value of 2.8 (reflecting the 86% lower C_{min} compared to 10 mg BID), respectively; error bars on filled squares and filled circle represent standard error. Black dotted arrow facilitates comparison of responses based on AUC_{24} and C_{min} values for 20 mg QD regimen.
%=percentage of responders; ACR=American College of Rheumatology; AUC_{24}=area under the concentration-time profile from time 0 to 24 hours; BID=twice daily; C_{min}=minimum plasma concentration; E_{max}=maximum drug effect; IR=immediate release; mg=milligrams; QD=once daily.

Black solid line represents posterior mean model prediction, black dashed line represents 80% prediction intervals from the model; black filled squares represent observed data for BID doses; red filled square and blue filled circle represent 20 mg QD data placed either at a x-axis value of 20 (reflecting the same AUC24 as 10 mg BID) or at a x-axis value of 2.8 (reflecting the 86% lower C_{min} compared to 10 mg BID), respectively.

Figure 1. Observed and Posterior Predicted Mean (10th-90th Percentile) Proportion of ACR20/50/70 Responders at Week 12 (Study A3921025)
(Source: Figure 4, Summary of Clin Pharm)

- **Safety:** All PK parameters for the MR 11 mg QD dose are equivalent (AUC and C_{max}) or slightly lower (29% lower C_{min}) as compared to those of the IR 5 mg BID dose. For MR 11 mg QD and IR 5 mg BID in RA patients at steady state, both doses cover the in-vitro JAK1/3 IC50 of 17 ng/mL for approximately 12 -13 hours over a 24-hour period, indicating a similar level of enzyme inhibition over the dosing interval (Figure 3).

  For the long term safety events, such as serious infection and malignancy, the information was all based on tofacitinib IR BID dosing regimens. The exposure-response for these adverse events (AE) is consistent with dose-response, and the tofacitnib concentration information did not provide additional explanation for these AEs. For short term safety profile as measured by LDL, HDL, serum creatinine, hemoglobin and absolute neutrophil counts, the data from 20 mg IR QD in study 1025 suggested that the short term safety profile with daily sustained inhibition of JAK for 12-13 hours is comparable to the inhibition of JAK under BID dosing regimen (Figure 2). Please refer to review by clinical reviewer Dr. Juwaria Waheed for further details of safety evaluation.

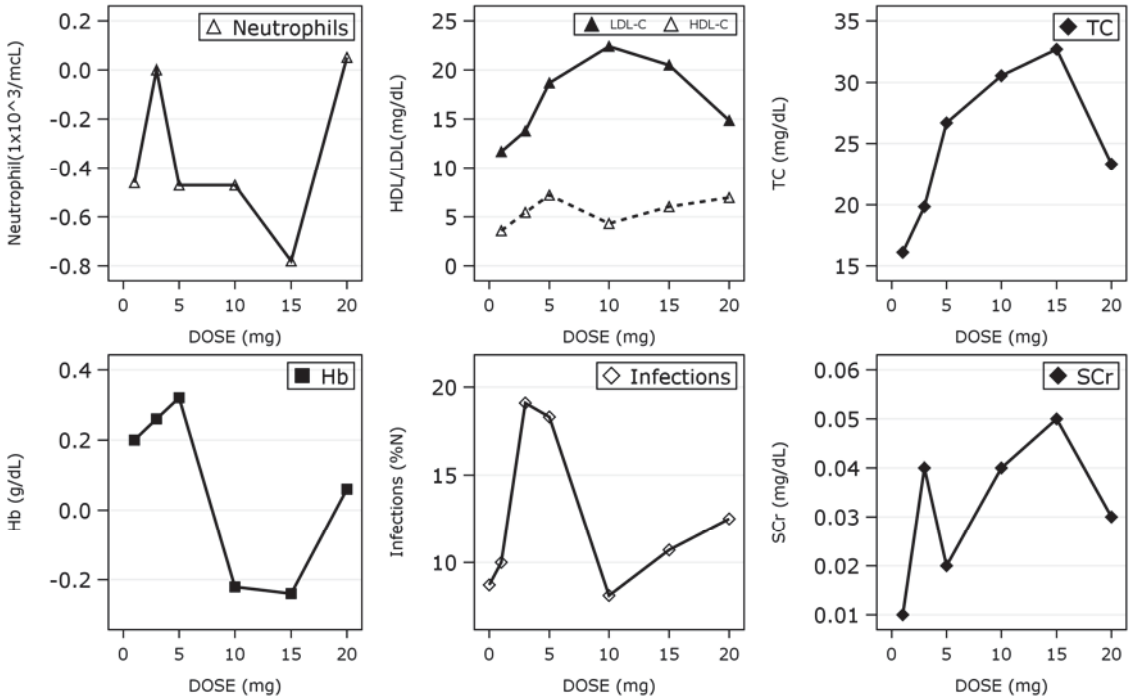


Figure 2: Dose-response relationship for safety endpoints from study 1025. Except infections all other endpoints are shown as placebo adjusted change from baseline to week 12 (delta baseline). Infections are reported as percent incidence at week 12. Except 20 mg QD all other doses were given in BID regimen (1, 3, 5, 10 and 15 mg BID).
(Source: Figure 19, NDA203214 Clin pharm review by Dr. Lokesh Jain)

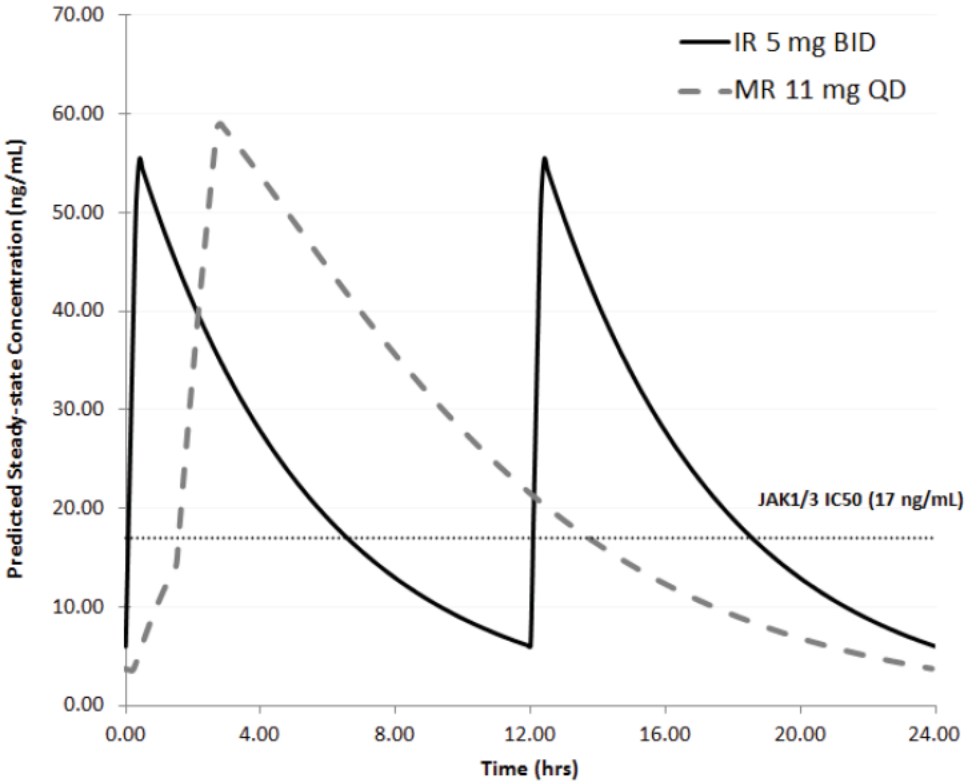


Figure 3. Predicted Steady State PK profiles in RA Patients Relative to JAK1/3 IC50

(Source: Figure 7, Summary Clin Pharm)

1.3.4 Special Population and Drug Interaction

In general, the aim of dose adjustment in special populations and DDIs is to produce a comparable PK profile and a comparable range of relevant PK parameters as the general population, to ensure the safety and efficacy of the drug in special populations. This may be achieved by a reduced dose, a prolonged dose interval, or combination of both. The dosing recommendation also considered the availability of different strength/ formulations, to make the treatment available for special populations.

The recommended dose is Tofacitinib IR 5 mg QD for:

- Patients with moderate to severe renal impairment
- Patients with moderate hepatic impairment (tofacitinib is not recommended for patients with severe hepatic impairment);
- Co-administration with potent inhibitors of cytochrome P450 (CYP3A4) (e.g., ketoconazole, (b) (4) or;
- Co-administration with 1 or more medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

While the sponsor proposed (b) (4) , tofacitinib concentrations on the first day of dosing (b) (4) in normal population, and tofacitinib concentrations on the second day (b) (4) than the

JAK1/3 IC50 of 17ng/mL. As tofacitinib IR 5 mg QD provided a much better PK profile (b) (4) in these populations(Figure 4), we recommend tofacitinib IR 5 mg QD for the above situations.

In addition to the 4 conditions described above, extension of IR formulation recommendations to the MR formulation includes clearance data by age, body weight, gender, race, CYP2C19 polymorphism, mild renal impairment or mild hepatic impairment and co-administration with rifampin. With the exception of rifampin, no dose modifications or restrictions are recommended. Co-administration of tofacitinib with rifampin and other potent inducers of CYP3A4 is not recommended.

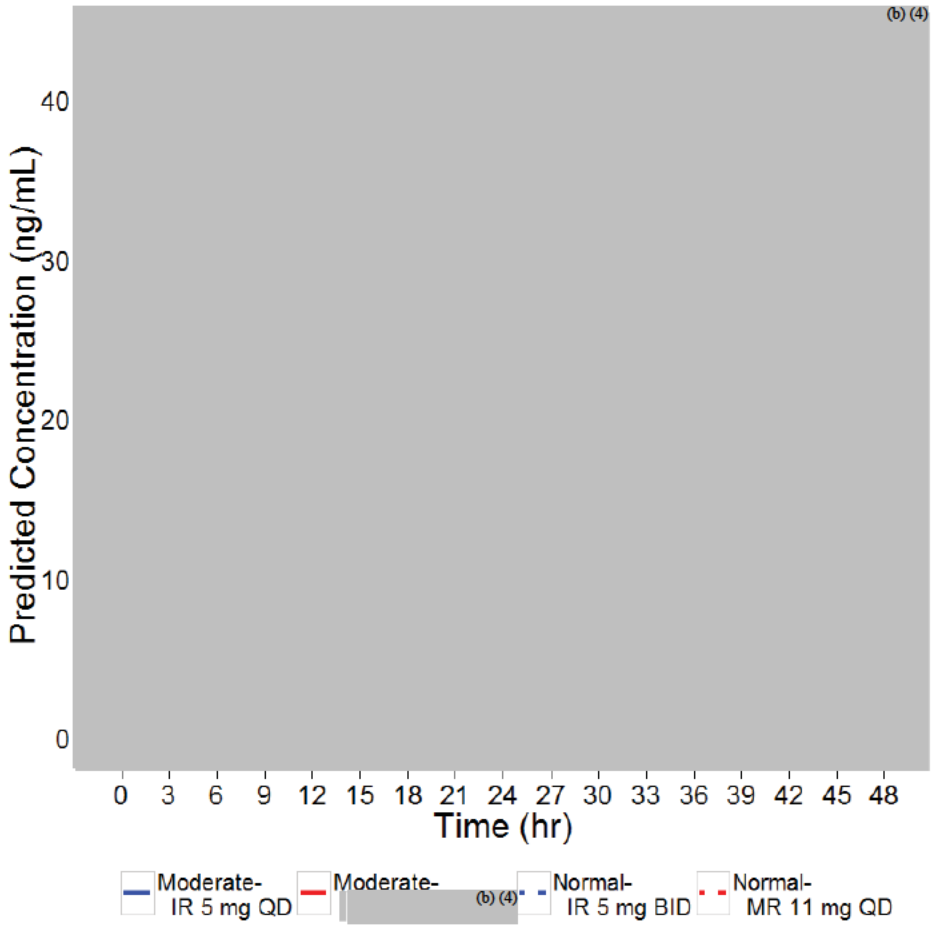


Figure 4. Simulated Tofacitinib Plasma Concentration-Time Profiles in Subjects with Normal Renal Function and Moderate Renal Impairment
(Source: Figure 9, Summary of clin pharm)

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

The MR clinical program was comprised of seven Phase 1 biopharmaceutic studies in healthy volunteers. These studies evaluated the following:

1. Feasibility of administering tofacitinib, a highly soluble drug, as an MR formulation (Study A3921113);
2. PK of pilot tofacitinib MR formulations (Studies A3921131 and A3921132);
3. Single dose PK and relative bioavailability (BA) of tofacitinib MR 11 mg tablets from an initial commercial-level scale manufacture, compared to IR 2x5 mg tablets (Study A3921163);
4. Effect of a high fat meal on the PK and BA of proposed-commercial tablet formulation of tofacitinib MR 11 mg (Study A3921180);
5. Single and multiple dose PK and relative BA of the proposed-commercial tablet formulation of tofacitinib MR 11 mg QD relative to IR 5 mg BID (Study A3921212);
6. Correlation of in-vitro dissolution with in-vivo plasma drug concentrations of MR tablet formulations with varying release rates (Study A3921195).

In addition, the sponsor provided exposure response analysis to establish the relevant PK parameter to bridge efficacy. The clinical pharmacology review focused on the six studies listed in item 1-5 above, and the exposure-response analysis for efficacy and safety. Please refer to review by Office of New Drug Quality Assessment (ONDQA) reviewer for assessment of study A3921195 and the in vitro alcohol dumping study.

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

The tofacitinib citrate IR film-coated tablet formulation has been approved in the United States (NDA203214) at a dose of 5 mg BID (Xeljanz®) for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate.

Pfizer has developed an MR 11 mg osmotic tablet formulation of tofacitinib, to provide a QD dosing option to IR 5 mg BID. There have been several interactions between Agency and Sponsor to discuss the overall development program for the proposed product as listed in Table 3.

OSI inspection was requested for study A3921212 (clinical site) and A3929023 (analytical lab), and the Division of New Drug Bioequivalence Evaluation (DNDBE) and Office of Study Integrity and Surveillance (OSIS) recommended to accept data without on-site inspection. See review by Dr. Shila Nkah dated 7/27/2015.

On 8/7/2015, a consult was sent to Office of Regulatory Policy, to seek ORP's input on the acceptability of an extended release formulation of tofacitinib (Xeljanz XR) with a nominal dose (11 mg once daily) different from the nominal dose of the immediate release formulation of tofacitinib (Xeljanz 5 mg twice daily, i.e. 10 mg total daily dose). Briefly, ORP suggested that as this is not a generic 505(j) submission, different daily doses were acceptable, and bioequivalence as stated in the 21CFR320.23 was not required or applicable for this submission. For further details with ORP consult, see Dr. Nikolay Nikolov's summary.

Table 3. Summary of Regulatory history relevant to clinical pharmacology

PNDA (Dec 2014)	Agreed on general clinical pharm studies adequate to support NDA filing. Recommend PK/PD analysis to include both QD and BID dosing regimen. Recommend PK/PD analysis to explore additional endpoints, such as ACR20, 50, 70.
Pre-IND (Mar 2013)	"Based on the PK profile and E-R, a clinical study may not add meaningful information and may not be necessary."

(Source: reviewer summary)

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The tofacitinib MR tablet uses ECS osmotic delivery technology to modify the release of tofacitinib in a controlled fashion, thereby enabling once-daily administration of tofacitinib. (b) (4) (b) (4)

Tofacitinib 11 mg modified release (MR) osmotic tablet formulation will be provided as oval, pink film-coated tablets with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet.

Tofacitinib MR 11 mg tablets contain 17.771 mg of tofacitinib citrate (equivalent to 11 mg of tofacitinib).

2.2.3 What are the proposed dosages and routes of administration?

The proposed dose is 11 mg once daily to be given orally.

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The tofacitinib MR clinical program consisted of 7 Phase 1 healthy volunteer (HV) studies that evaluated the PK of multiple pilot formulations and the proposed commercial MR 11 mg formulation for QD dosing. No new efficacy or safety studies have been conducted in RA patients using the tofacitinib MR formulation in support of this application. The clinical pharmacology and biopharmaceutics studies supporting this NDA and their design features are listed under section 2.1.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The tofacitinib MR clinical pharmacology program has demonstrated equivalent AUC and C_{max} for the MR 11 mg QD formulation compared to the currently approved Xeljanz® (IR 5 mg BID) formulation. Based on exposure-response (E-R) analysis, C_{av} (AUC) is the most relevant PK parameter to predict efficacy.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. In all relevant studies only tofacitinib concentrations were measured. No metabolites were quantified because exposure of each metabolite was <8% of total tofacitinib exposure and their potency for JAK1/JAK3 inhibition was reported to be ≤10% compared to parent.

2.4 Exposure-Response

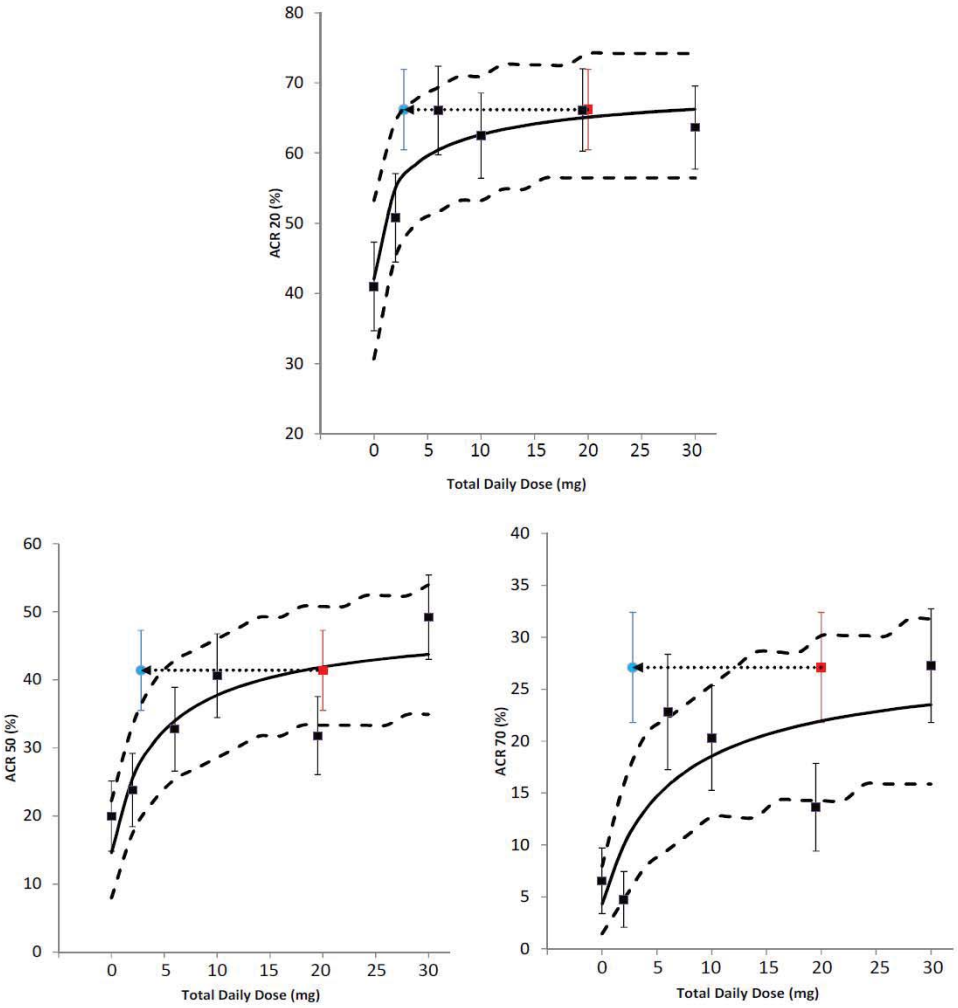
2.4.1 What are the characteristics of the exposure-response relationship for effectiveness?

The PK profile of the MR formulation, demonstrating overall similarity in PK parameters, with equivalent AUC and C_{max}, and 29% lower C_{min} compared to the approved IR dosing regimen. The observed data and application of PK/PD modeling approaches consistently showed that Cav appears to be the most relevant parameter for efficacy and that the 29% lower Cmin for the MR formulation may not be clinically important to the efficacy of tofacitinib.

The importance of C_{min} to the efficacy of tofacitinib was assessed using data from Study A3921025, a Phase 2B double-blind study of placebo and IR 1, 3, 5, 10, 15 mg BID and 20 mg QD doses of tofacitinib. Following administration of the same total daily dose in two different regimens (i.e. IR 20 mg QD or IR 10 mg BID), AUC_{24} was similar between the two regimens (within 10%), while C_{min} was approximately 7-fold (86%) lower and C_{max} was approximately 2-fold higher for the IR 20 mg QD dose compared to the IR 10 mg BID dose, respectively. Despite a large difference in C_{min}, the efficacy (measured by DAS28 improvements or American College of Rheumatology [ACR]20/50/70 responses at Week 12) of the IR 20 mg QD dose was similar to that of the IR 10 mg BID dose and consistent with the predicted BID dose response profiles across these endpoints (Figure 5, Figure 6). The C_{min} difference observed in Study A3921025 is substantially larger than the 29% lower C_{min} observed for MR 11 mg QD compared to IR 5 mg BID in the MR program, supporting that this C_{min} difference is not clinically important to the efficacy of tofacitinib when there is equivalent AUC.

To characterize the most relevant tofacitinib PK parameter for efficacy and assess the predictive value of C_{min} over and above C_{av}, E-R analyses were conducted using DAS28 and ACR 20, 50, 70 responses at Week 12 from the pooled Phase 2 studies (A3921025, A3921035, A3921039, and A3921040) of the IR RA program. Comparison of the goodness of fit characteristics as measured by OFV or AIC for models with different PK parameters (C_{av} vs. C_{max} vs C_{min}) supported C_{av} as the most relevant PK parameter for efficacy. Furthermore, C_{min} did not provide additive predictive value over and above that of C_{av} in this analysis.

The totality of E-R evidence from the tofacitinib IR RA program, combined with demonstrated equivalence for AUC and C_{max} between the MR and IR formulations, support bridging of efficacy data derived using the IR 5 mg BID formulation to the MR 11 mg QD formulation.



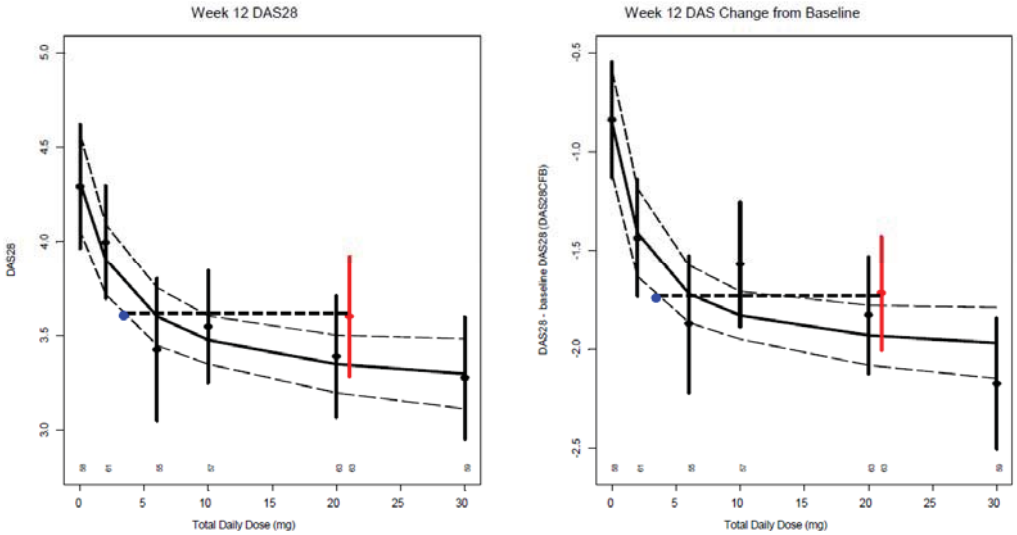
The observed proportion of ACR20/50/70 responders for IR 20 mg QD dose at Week 12 is overlaid with model-predicted posterior mean (10^{th}-90^{th} percentiles) from a longitudinal E_{max} model applied to BID doses in Study A3921025. Doses are presented on a total daily dose scale.

Black solid line represents posterior mean model prediction, black dashed line represents 80% prediction intervals from the model; black filled squares represent observed data for BID doses; red filled square and blue filled circle represent 20 mg QD data placed either at a x-axis value of 20 (reflecting the same AUC_{24} as 10 mg BID) or at a x-axis value of 2.8 (reflecting the 86% lower C_{min} compared to 10 mg BID), respectively; error bars on filled squares and filled circle represent standard error. Black dotted arrow facilitates comparison of responses based on AUC_{24} and C_{min} values for 20 mg QD regimen.

%=percentage of responders; ACR=American College of Rheumatology; AUC_{24}=area under the concentration-time profile from time 0 to 24 hours; BID=twice daily; C_{min}=minimum plasma concentration; E_{max}=maximum drug effect; IR=immediate release; mg=milligrams; QD=once daily.

Figure 5. Observed and Posterior Predicted Mean (10th-90th Percentile) Proportion of ACR20/50/70 Responders at Week 12 (Study A3921025)

(Source: Figure 4, Summary of Clin Pharm)



The 95% CI for the efficacy endpoints of the IR 20 mg QD dose relative to placebo and IR BID doses is overlaid with model-predicted 95% CI band for DAS28 response at Week 12. Doses are presented on a total daily dose scale.
Black solid line represents typical model prediction, black dotted line represents 95% CI of the model prediction; red filled circle represents 20 mg QD data; black filled circles represents BID data; error bars on filled circles represent empirical 95% CIs. The numbers above the x-axis inside the plots represent the number of patients at each dose level. DAS28CFB represents difference of DAS28 at Week 12 and baseline DAS28.
CFB=change from baseline; CI=confidence interval; DAS=disease activity score; IR=immediate release; mg=milligrams; Pred= typical model prediction; QD=once daily; RA=rheumatoid arthritis.

Figure 6. Dose-Response Relationship of DAS28 at Week 12 in RA Patients Receiving Tofacitinib Twice Daily Using IR Tablets (Study A3921025)
(Source: Figure 3, Summary of Clin Pharm)

2.4.2 What are the characteristics of the exposure-response relationships for safety?

All PK parameters for the MR 11 mg QD dose are equivalent (AUC and C_{max}) or slightly lower (29% lower C_{min}) as compared to those of the IR 5 mg BID dose. Benchmarking the expected tofacitinib exposures for MR 11 mg QD and IR 5 mg BID in RA patients against JAK inhibition, both doses cover the in-vitro JAK1/3 IC50 of 17 ng/mL (reported as 56 nM by Meyer et al, 2010) for approximately 12 -13 hours over a 24-hour period, indicating a similar level of enzyme inhibition over the dosing interval (Figure 7).

The data from 20 mg IR QD in study 1025 suggested that the short term safety profile with once daily sustained inhibition of JAK1/3 for 12-13 hours is comparable to the BID dosing regimen. Short term safety of tofacitinib, as measured by laboratory parameters such as LDL, HDL, serum creatinine, and absolute neutrophil counts at 12 weeks, is dose dependent. A trend of decrease in neutrophil counts and increase in LDLC, HDLC, total cholesterol and serum creatinine was observed with increase in BID tofacitnib doses (1-15 mg BID) in study1025 (Figure 8, on background of MTX). However, the 20 mg QD dose appears to have better safety profiles as measured by these laboratory parameters, compared to 10 mg BID (Figure 8).

For the long term safety events, such as serious infection and malignancy, the AE information was all based on BID dosing regimens, and the PK parameters (C_{max}, C_{min} and C_{av}) were highly correlated. As the sponsor stated, the exposure response is consistent with dose response, and the tofacitnib concentration information did not

provide additional explanation for the AEs. Please refer to review by medical officer Dr. Juwaria Waheed for further details of safety evaluation.

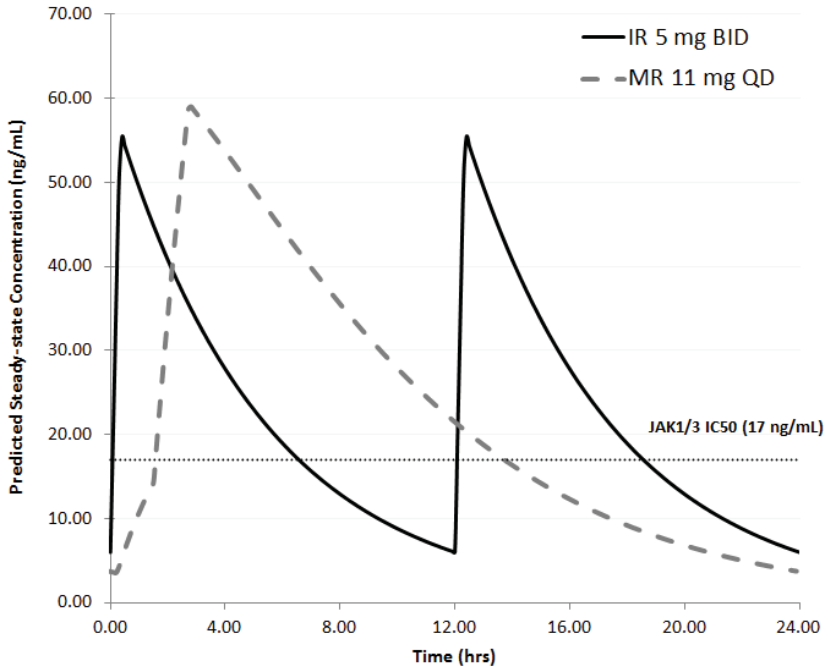


Figure 7. Predicted Steady State PK profiles in RA Patients Relative to JAK1/3 IC50

(Source: Figure 7, Summary Clin Pharm)

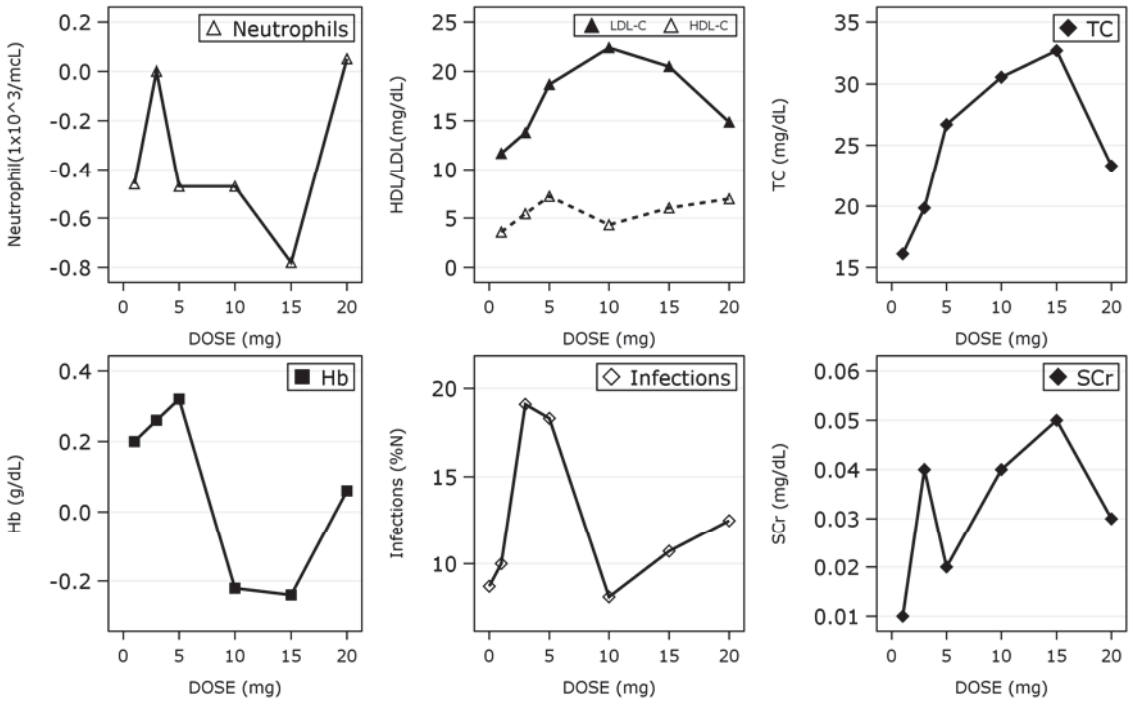


Figure 8: Dose-response relationship for safety endpoints from study 1025. Except infections all other endpoints are shown as placebo adjusted change from baseline to week 12 (delta baseline). Infections are reported as percent incidence at week 12. Except 20 mg QD all other doses were given in BID regimen (1, 3, 5, 10 and 15 mg BID).
(Source: Figure 19, NDA203214 Clin pharm review by Dr. Lokesh Jain)

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Single dose PK

Following administration of tofacitinib MR 11 mg (single oral dose) and tofacitinib IR 10 mg (2 tablets of 5 mg administered approximately 12 hours apart), peak concentrations after the morning dose (C_{max} for MR and $C_{max}1$ for IR) were similar. Peak concentrations were reached later for the MR treatment (median T_{max} = 4 hours) than for the IR treatment (median $T_{max}1$ = 0.5 hours) and terminal half-life was longer for the MR formulation (mean 5.9 hours) compared to the IR formulation (mean 3.2 hours). Total plasma tofacitinib exposure based on geometric mean AUC_{inf} was similar for both treatments (Table 4).

The extent of exposure for a single dose of tofacitinib MR 11 mg was equivalent to the total dose of tofacitinib IR 10 mg administered as two 5 mg doses approximately 12 hours apart, based on the 90% CI for the ratio (MR/IR) of adjusted geometric means for AUC_{inf} and C_{max} being within equivalence limits (80% to 125%, Table 4).

Table 4. Statistical Summary of Treatment Comparisons for Plasma Tofacitinib Parameters Following a Single Oral Dose of Tofacitinib MR 11 mg and 2 Separate Oral Dose Administrations of Tofacitinib IR 5 mg (12 hours apart) on Day 1

	Adjusted Geometric Means			
Parameter (units)	Tofacitinib MR 11 mg (Test)	Tofacitinib IR 10 mg (5 mg BID) (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng.hr/mL)	253.2	243.7	103.92	98.81, 109.28
AUC_{last} (ng.hr/mL)	250.8	241.4	103.90	98.87, 109.19
C_{max}[b] (ng/mL)	35.98	39.22	91.75	83.27, 101.09

(Source: Table13, study A3921212 CSR)

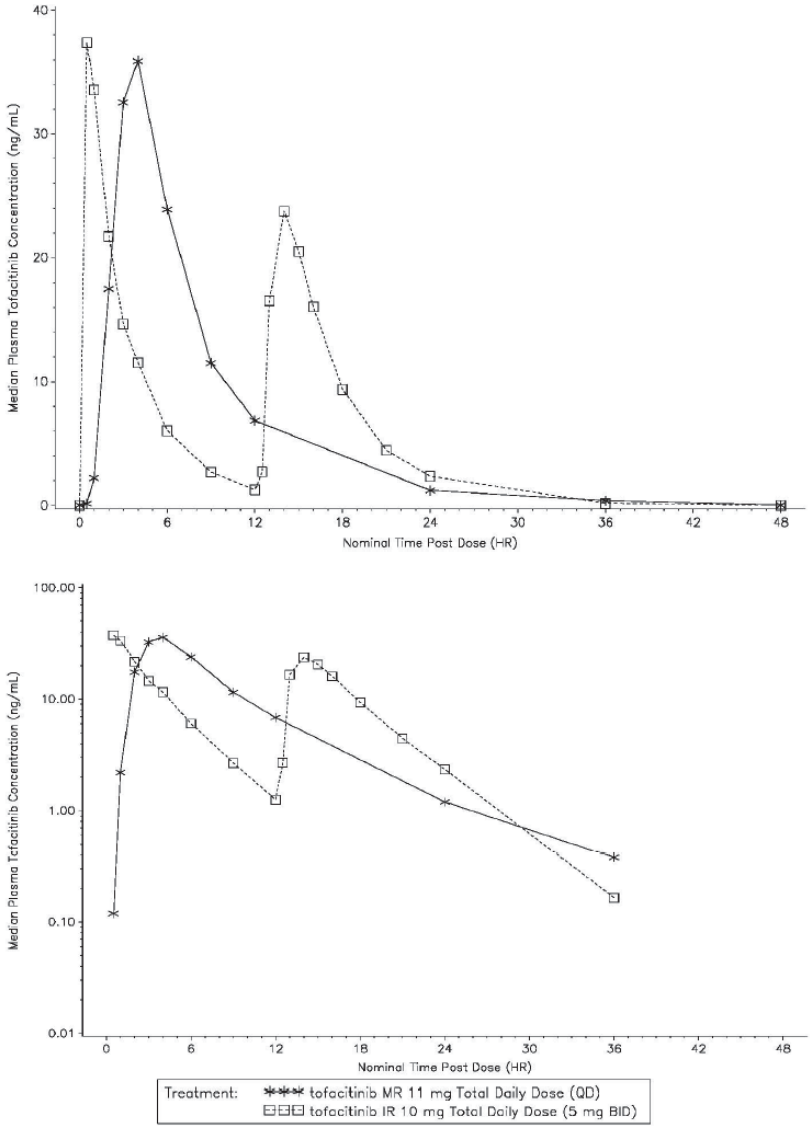


Figure 9: Median Plasma Tofacitinib Concentration-Time Profiles Following a Single Oral Dose of Tofacitinib MR 11 mg and Two Separate Oral Dose Administrations of Tofacitinib IR 5 mg (12 hours apart) on Day 1

(Source: Figure 2, study report A3921212)

Multiple dose PK

Following administration of tofacitinib MR 11 mg QD and tofacitinib IR 5 mg BID for 5 days, the overall results were consistent with those described above for Day 1 (single dose phase). Total daily plasma tofacitinib exposure based on AUC_{24} was similar for both treatments. Peak concentrations for Day 7 (C_{max} for MR and $C_{max}1$ for IR) were also similar with median T_{max} of 4 hours for MR and median $T_{max}1$ of 0.5 hours for IR, the same as on Day 1. Following the second tofacitinib IR 5 mg dose at 12 hours, peak (evening) concentrations for the IR treatment ($C_{max}2$) were approximately 20% lower than peak ($C_{max}1$) after the morning dose and were reached slightly later with median $T_{max}2$ observed 1 hour post-evening dose (13 hours post-morning dose).

Results of the statistical analysis are summarized in Table 5. The 90% CIs for the ratio (MR/IR) of adjusted geometric means for AUC_{24} and C_{max} values (C_{max} for MR and C_{max1} for IR) were within the 80% to 125% interval, demonstrating equivalence of tofacitinib total daily exposure for tofacitinib MR 11 mg QD and tofacitinib IR 5 mg BID.

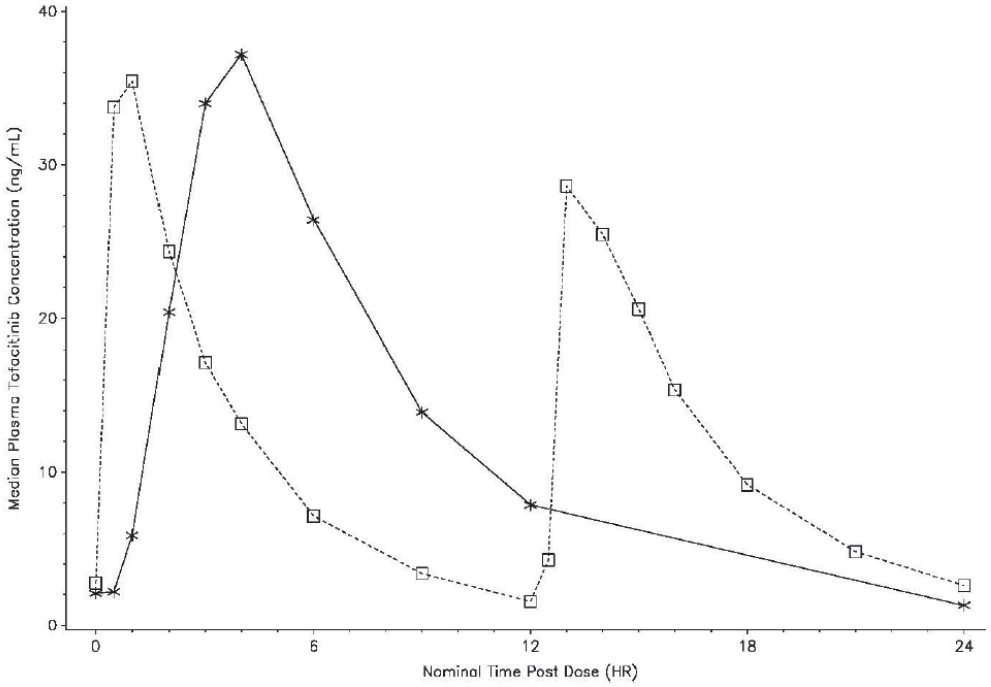


Figure 10. Median Plasma Tofacitinib Concentration-Time Profiles For Tofacitinib MR 11 mg Once Daily and Tofacitinib IR 5 mg BID on Day 7 (Day 5 of Multiple Dosing)
(Source: Figure 4, study A3921212 CSR)

Table 5. Statistical Summary of Treatment Comparisons for Plasma Tofacitinib Parameters for Tofacitinib MR 11 mg QD and Tofacitinib IR 5 mg BID on Day 7 (Day 5 of Multiple Dosing)

	Adjusted Geometric Means			
Parameter (units)	Tofacitinib MR 11 mg QD (Test)	Tofacitinib IR 5 mg BID (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{24} (ng.hr/mL)	268.5	263.4	101.94	97.79, 106.27
C_{max}[b] (ng/mL)	38.19	40.89	93.41	84.14, 103.69
C_{trough} (ng/mL)	1.820	2.475	73.54	57.71, 93.70
C_{min}[b] (ng/mL)	1.044	1.478	70.64	59.01, 84.56

(Source: Table15, study A3921212 CSR)

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Studies A3921132 evaluated dose proportionality for ECS osmotic MR formulation in the fasted state. MR 11 mg (QD equivalent of IR 5 mg BID) and MR 22 mg (QD equivalent of IR 10 mg BID) demonstrated dose-proportional exposures (Table 6).

Table 6. Descriptive Summary of Plasma Tofacitinib Pharmacokinetic Parameter Values for MR 11 mg Tablets and MR 22 mg Tablets

	Parameter Summary Statistics[a] by Treatment	
Parameter (units)	**MR 11 mg (Test)**	**MR 22 mg (Reference)**
N	20	20
AUC_{inf} (ng.hr/mL)	315.6 (21)	645.8 (23)
AUC_{last} (ng.hr/mL)	313.7 (21)	641.1 (23)
C_{max} (ng/mL)	42.20 (32)	84.43 (22)
T_{max} (hr)	3.00 (2.00-4.00)	3.00 (2.00-4.00)
$t_{½}$ (hr)	6.250 ± 2.280	7.295 ± 3.375
$AUC_{inf\,(dn)}$ (ng.hr/mL/mg)	28.68 (21)	29.35 (23)
$AUC_{last\,(dn)}$ (ng.hr/mL/mg)	28.52 (21)	29.14 (23)
$C_{max\,(dn)}$ (ng/mL/mg)	3.837 (32)	3.838 (22)

(Source: Table 12, study A3921132 CSR)

2.5.14 Is there evidence for a circadian rhythm of the PK?

Following the second tofacitinib IR 5 mg dose at 12 hours, peak (evening) concentrations for the IR treatment ($C_{max}2$) were approximately 30% lower than peak ($C_{max}1$) after the morning dose (Figure 9 and Figure 10) and were reached more slowly, with median $T_{max}2$ observed 2 hours post-evening dose (14 hours post-morning dose).

Geometric mean AUC for the 0 to 12 hour, and 12 hour to 24 hour dosing interval (AUCτ) values following the morning and evening doses of the tofacitinib IR 5 mg dose were similar (Table 7, 115.8 ng.hr/mL and 118.4 ng.hr/mL, respectively on day 1; Table 31, 131.6 ng.hr/mL and 131.5 ng.hr/mL, respectively on day 5).

Table 7. Descriptive Summary of Plasma Tofacitinib Pharmacokinetic Parameter Values for a Single Oral Dose of Tofacitinib MR 11 mg and Two Separate Oral Dose Administrations of Tofacitinib IR 5 mg (12 hours apart) on Day 1

	Parameter Summary Statistics[a] by Treatment			
	Tofacitinib MR 11 mg Total Daily Dose	**Tofacitinib IR 10 mg Total Daily Dose (5 mg BID)**		
Parameter (Unit)	**All Data (0-48 hr)**	**All Data (0-48 hr)**	**Interval 1 Morning 0-12 hr[b]**	**Interval 2 Evening 12-24 hr[b]**
N	23	24	24	24
AUC_{inf} (ng.hr/mL)	253.3 (24)	243.7 (20)	NA	NA
AUC_{last} (ng.hr/mL)	250.9 (24)	241.4 (20)	NA	NA
AUC_{24} (ng.hr/mL)	241.1 (22)	234.2 (19)	NA	NA
$AUC_{τ}$ (ng.hr/mL)[c]	241.1 (22)	NA	115.8 (20)	118.4 (19)
$t_{½}$ (hr)	5.890±1.807	3.208±0.814	NA	NA
C_{max} (ng/mL)	36.10 (18)	40.15 (24)	39.22 (27)	27.96 (21)
T_{max} (hr)	4.00 (3.00-4.02)	0.500 (0.500-13.0)[d]	0.500 (0.500-1.00)	2.00 (0.5- 4.00)[e]

(Source: Table 12, study A3921212 CSR)

2.6 Intrinsic Factors

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Dosing adjustments with the tofacitinib MR 11 mg formulation for subjects with renal or hepatic impairment and for drug-drug interactions (DDIs) with potent CYP3A4 inhibitors such as ketoconazole and moderate CYP3A4 and potent CYP2C19 inhibitors such as fluconazole were derived based on a modeling and simulation approach.

The PK model for the IR and MR formulation was established with the data from study A3921212. To simulate the plasma concentration-time profile in special populations and in presence of co-administered drugs, it is assumed that the fractional changes in CL/F observed from the individual clinical pharmacology studies of the IR formulation were applicable to the MR formulation.

The daily exposure at steady state for each population with proposed dosing regimens were summarized based on simulation data using WinNonlin version 5.2.1. These simulated concentration – time profiles for alternative dosing regimens were used to guide dosing recommendations by matching the daily exposure.

Reviewer's comment
In the IR to MR transition, it is reasonable to assume the same fractional changes in CL/F for the intrinsic factors and DDIs.

2.6.2.6 Renal Impairment

Based on study A3921006 with the tofacitinib IR formulation, subjects with mild, moderate, and severe renal impairment had 41% (-6%, 112%), 71% (13%, 159%), and 150% (61%, 287%) respective increase in AUC compared to subjects with normal renal function. Utilizing the mean AUC_{inf} ratios, the mean clearance ratios (renal impairment vs. normal renal function) were 58% and 40% for moderate and severe renal impairment, respectively.

Assuming the same fractional changes in CL/F for tofacitinib MR, The simulated plasma concentration-time profiles for the [redacted] (b) (4) are shown in Figure 11 (moderate renal impairment) and Figure 12 (severe renal impairment) along with those of the IR 5 mg QD dose. The resulting PK parameters from this simulation are shown in Table 8.

Table 8: Steady-state PK parameters calculated based on simulated profiles for subjects with normal renal function or renal impairment

Population	Dose	Dosing Regimen	AUC_{0-48} ng/mL*hr	AUC_{0-24} ng/mL*hr	AUC_{24-48} ng/mL*hr	C_{max} ng/mL
Normal	5 mg	BID	552	276	276	36.4
	11 mg	QD	558	279	279	38.9
Moderate Renal Impairment	5 mg	QD	475	237	237	37.3
	[redacted]					(b) (4)
Severe Renal Impairment	5 mg	QD	687	343	344	39.8
	[redacted]					(b) (4)

(Source: Reviewer analysis)

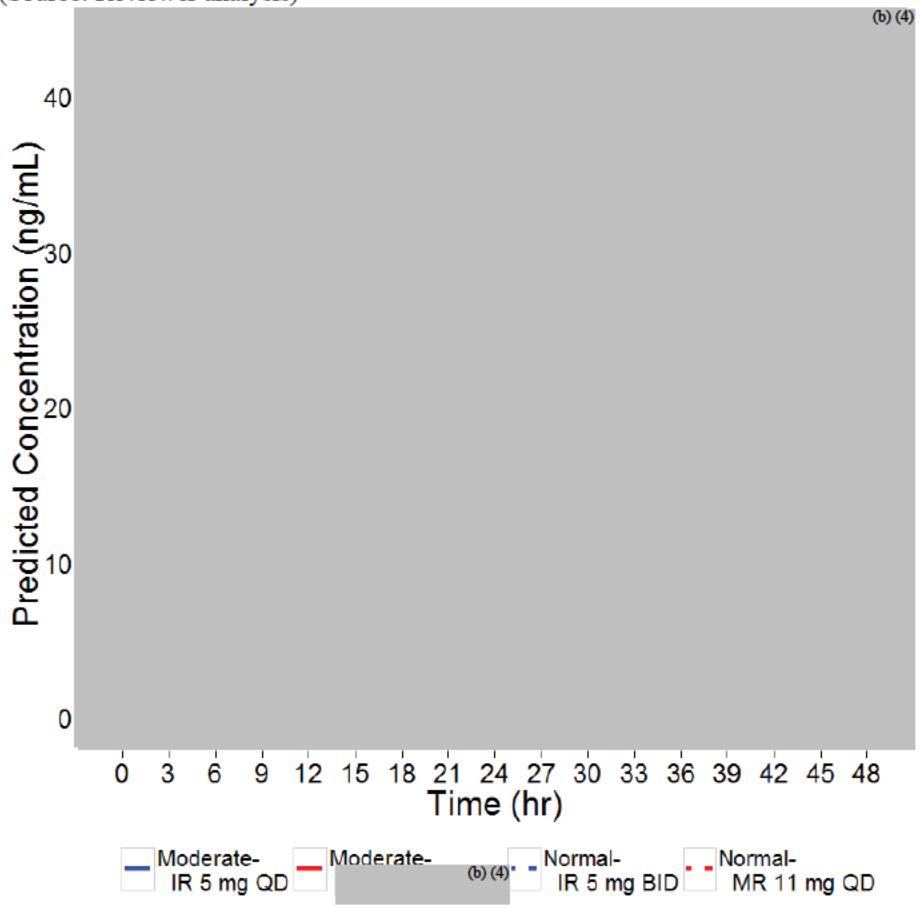


Figure 11. Simulated Tofacitinib Plasma Concentration-Time Profiles in Subjects with Normal Renal Function and Moderate Renal Impairment
(Source: Figure 9, Summary of clin pharm)

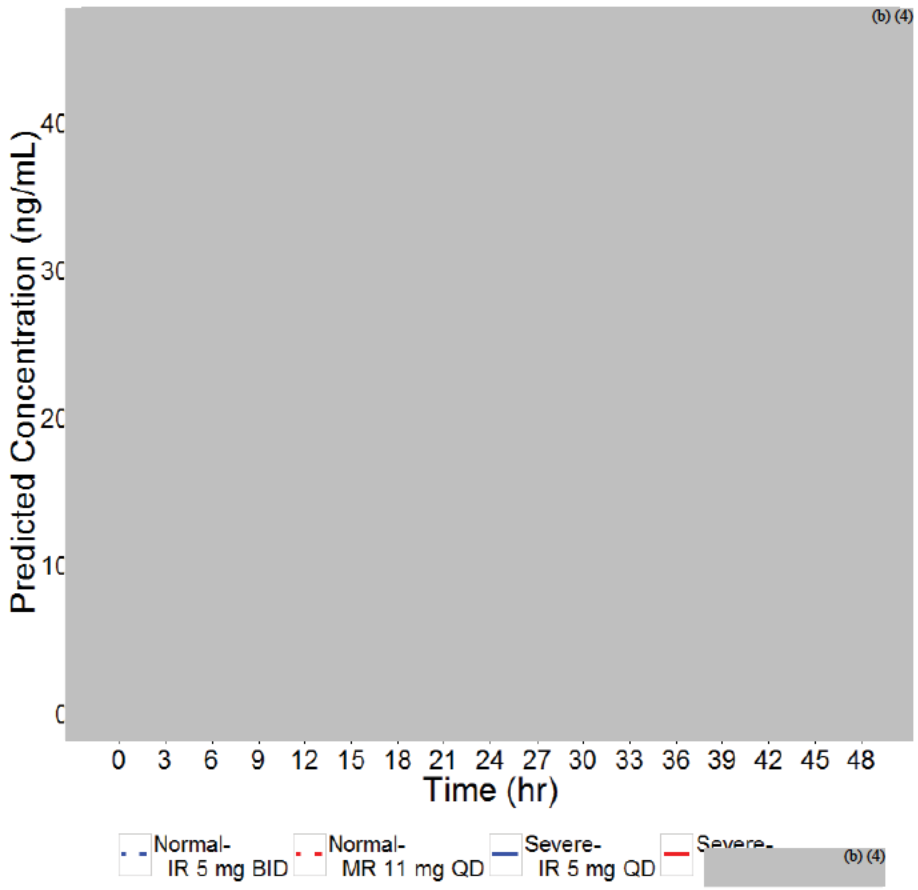


Figure 12. Simulated Tofacitinib Plasma Concentration-Time Profiles in Subjects with Normal Renal Function and Severe Renal Impairment
(Source: Figure 10, Summary of clin pharm)

2.6.2.7 Hepatic Impairment

Mild hepatic impairment (Child Pugh A) did not alter tofacitinib exposure compared to subjects with normal hepatic function. No dose adjustments are recommended for mild hepatic impairment.

In subjects with moderate hepatic impairment (Child Pugh B), there was a 65% increase in tofacitinib AUC_{inf} (90% CI 24.95%, 116.75%) and a 49% increase in C_{max} (90% CI 12.26%, 97.11%) compared to subjects with normal hepatic function. Utilizing the mean AUC_{inf} ratios, the mean clearance ratio (moderate hepatic impairment vs. normal hepatic function) was 61%.

Assuming the same fractional changes in CL/F for tofacitinib MR, The simulated plasma concentration-time profiles for (b) (4) in patients with moderate hepatic impairment are shown in Figure 13 along with those of the IR 5 mg QD dose. The resulting PK parameters from this simulation are shown in Table 9.

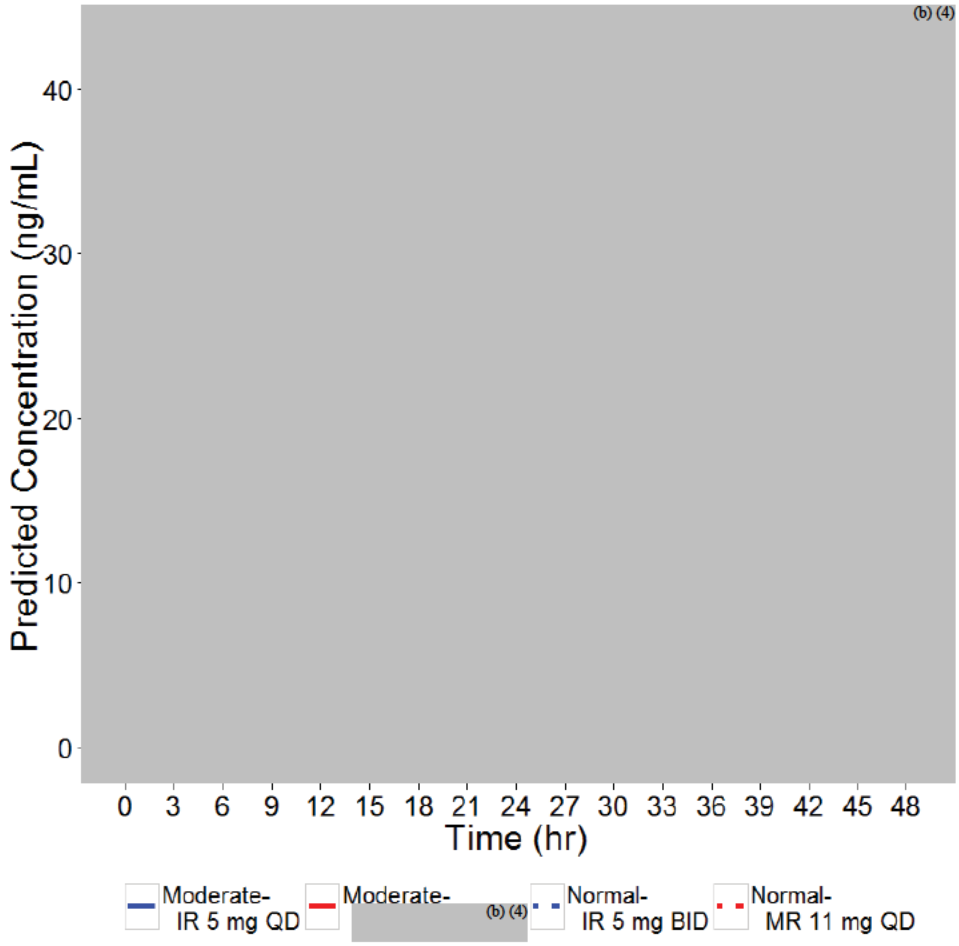


Figure 13. Simulated plasma concentration-time profiles for subjects with normal hepatic function and moderate hepatic impairment
(Source: Figure 11, Summary of clin pharm)

Table 9: Steady-state PK parameters calculated based on simulated profiles for subjects with normal hepatic function or hepatic impairment

Population	Dose	Dosing Regimen	AUC_{0-48} ng/mL*hr	AUC_{0-24} ng/mL*hr	AUC_{24-48} ng/mL*hr	C_{max} ng/mL
Normal	5 mg	BID	552	276	276	36.4
	11 mg	QD	558	279	279	38.9
Moderate Hepatic Impairment	5 mg	QD	452	226	226	37
						(b) (4)

(Source: Reviewer analysis)

2.7 Extrinsic Factors

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

The effect of coadministration with other drugs on tofacitinib exposure has been evaluated for tofacitinib IR, and the dose adjustment of tofacitinib was recommended when tofacitinib is coadministered with ketoconazole or fluconazole (Table 10).

Table 10: Effect of coadministered drugs on tofacitinib

Coadministered drug	Tofacitinib	GMR (90% CI)	
		AUC	C_{max}
Ketoconazole (potent P-gp and CYP3A4 inhibitor) 400 mg QD (monotherapy: days 1 and 2, with tofacitinib on day 3)	Tofacitinib 10 mg (test arm: coadministered with ketoconazole on day 3; reference arm: single-dose on day 1)	203.2 (191-216.3)	116.2 (104.6-129.2)
Fluconazole (moderate inhibitor of CYP3A4 and potent inhibitor of CYP2C19) (400 mg QD loading dose on day 1, followed by 200 mg QD from days 2 to 7)	Tofacitinib 30 mg (test arm: coadministered with fluconazole on day 5; reference arm: single-dose on day 1)	179.3 (163.8-196.2)	126.7 (111.8-143.7)

(Source: Table 19, NDA203214 Clin pharm review by Dr. Lokesh Jain)

Fluconazole:

Co-administration of tofacitinib with fluconazole increased the AUC and C_{max} of tofacitinib by 79% (90% CI for increase: 64%-96%) and 27% (90% CI for increase: 12%-44%), respectively, relative to tofacitinib alone. Utilizing the mean AUC_{inf} ratios, the mean clearance ratio (tofacitinib + fluconazole vs. tofacitinib alone) was 56%.

The simulated plasma concentration-time profiles for (b) (4) are shown in Figure 12 along with those of the IR 5 mg QD dose. The resulting PK parameters from this simulation are shown in Table 11.

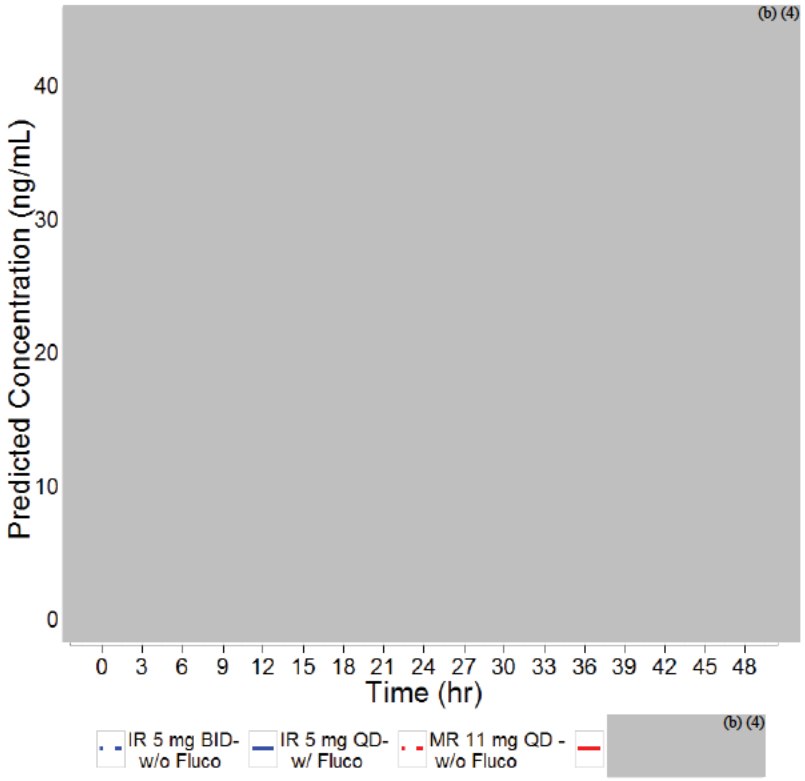


Figure 14. Simulated Tofacitinib Plasma Concentration-Time Profiles for Various Regimens with or without Fluconazole

(Source: Figure 12, Summary of clin pharm)

Table 11: Steady-state PK parameters calculated based on simulated profiles with and without fluconazole

Population	Dose	Dosing Regimen	AUC_{0-48} ng/mL*hr	AUC_{0-24} ng/mL*hr	AUC_{24-48} ng/mL*hr	C_{max} ng/mL
Without ketoconazole	5 mg	BID	552	276	276	36.4
	11 mg	QD	558	279	279	38.9
With ketoconazole	5 mg	QD	494	247	247	37.5
						(b) (4)

(Source: Reviewer analysis)

Ketoconazole:

The simulated plasma concentration-time profiles for (b) (4) are shown in Figure 15 along with those of the IR 5 mg QD dose. The resulting PK parameters from this simulation are shown in Table 12.

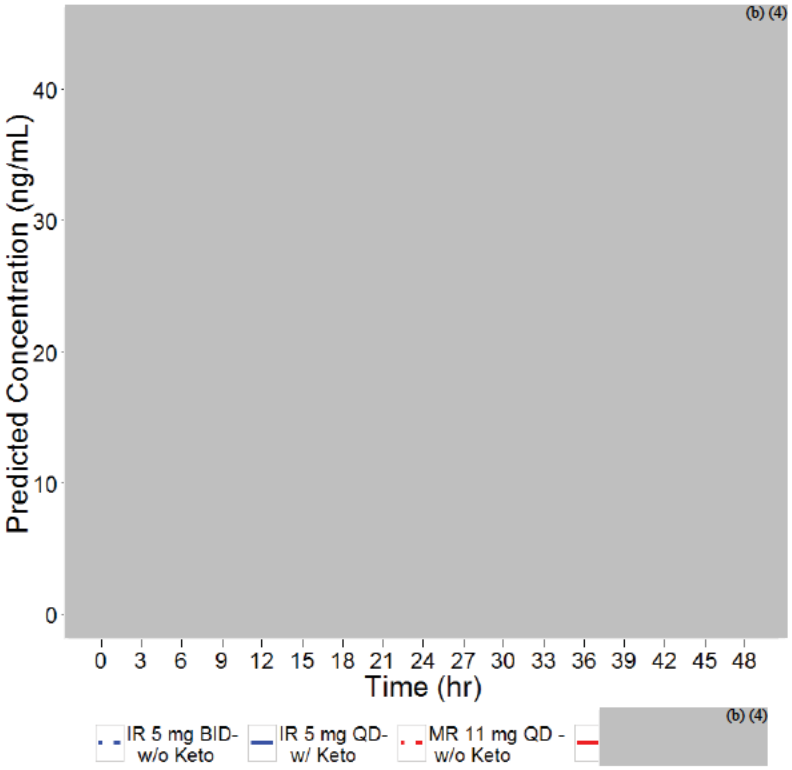


Figure 15: Simulated Tofacitinib Plasma Concentration-Time Profiles for Various Regimens with or without Ketoconazole

(Source: Figure 14, Summary of clin pharm)

Table 12: Steady-state PK parameters calculated based on simulated profiles with and without ketoconazole

Population	Dose	Dosing Regimen	AUC_{0-48} ng/mL*hr	AUC_{0-24} ng/mL*hr	AUC_{24-48} ng/mL*hr	C_{max} ng/mL
Without ketoconazole	5 mg	BID	552	276	276	36.4
	11 mg	QD	558	279	279	38.9
With ketoconazole	5 mg	QD	559	279	280	38.2
						(b) (4)

(Source: Reviewer analysis)

Reviewer's comments

1. The simulated concentration – time profiles for alternative dosing regimens were used to guide dosing recommendations. AUC and C_{max} for simulated profiles were calculated by non-compartmental analysis and were taken into account while identifying an alternative dosing regimen. Doses were adjusted to match the daily exposures (AUCs) to that obtained after administration of tofacitinib IR 5 mg BID or tofacitinib MR 11 mg QD in general population as single therapy.

2. The recommended dose is tofacitinib IR 5 mg QD for:
   - Patients with moderate to severe renal impairment;
   - Patients with moderate hepatic impairment (tofacitinib is not recommended for patients with severe hepatic impairment);
   - Co-administration with potent inhibitors of cytochrome P450 (CYP3A4) (e.g., ketoconazole, (b) (4) or;
   - Co-administration with 1 or more medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

3. While the sponsor proposed (b) (4) , tofacitinib concentrations on the first day (b) (4) in normal population, and tofacitinib concentrations on the second day (b) (4) than the JAK1/3 IC50 of 17ng/mL. As tofacitinib IR 5 mg QD provided a much better PK profile (b) (4) (Figure 13), we recommend tofacitinib IR 5 mg QD for the above situations.

2.8 General Biopharmaceutics

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

The pivotal PK study A3921212 and food effect study A3921180 were done with the to-be-marketed commercial formulation. Osmotic capsules with different release durations of tofacitinib were evaluated in the initial controlled release feasibility study, A3921113. Subsequently, (b) (4) tablets and Extrudable Core System (ECS) osmotic tablets were evaluated in A3921131 to select the appropriate controlled release technology/platform for further development. The ECS osmotic tablet platform was selected for further clinical and commercial development and was used to support studies A3921132, A3921163, A3921180, A3921195, and A3921212. The compositions of the ECS osmotic clinical and proposed-commercial tofacitinib MR tablets are summarized in Table 13. Please refer to review by Office of New Drug Quality Assessment (ONDQA) reviewer for further details on formulation development.

Table 13: Composition of Tofacitinib MR Tablets Extrudable Core System (ECS) Used in Phase 1 Biopharmaceutic Studies

	MR 22 mg (Clinical Formulations)		MR 11 mg (Clinical Formulations)					MR 11 mg (Proposed-Commercial Formulation)
Identity Code	D1100287	D1306654	D1200082	D1306446	D1306632	D1306652	D1306651	D1306633
Description[a]	22 mg (b) (4)	22 mg (b) (4)	11 mg (b) (4)	11 mg (b) (4)	11 mg pink, film-coated tablets, (b) (4)	11 mg pink, film-coated tablet (b) (4)	11 mg pink, film-coated tablet, (b) (4)	11 mg pink, film-coated tablets, printed
Studies Supported	A3921131, A3921132	A3921195	A3921132	A3921163	A3921195	A3921195	A3921195	A3921180, A3921212
Drug Loading (% DS)	(b) (4)							
Shape	Oval	Oval	Oval	Oval	Oval	Oval	Oval	Oval
(b) (4)								
Tofacitinib Citrate (mg)	(b) (4)			17.771	17.771	17.771	17.771	17.771
Sorbitol (mg)								(b) (4)
Hydroxyethyl Cellulose (mg)								
Copovidone (mg)								
Colloidal Silicon Dioxide (mg)								
Magnesium Stearate (mg)								
(b) (4)								(b) (4)
Cellulose Acetate (mg)								
(b) (4)								
(b) (4)								
(b) (4)								
Printing								
(b) (4)	-	-	-	-		-	-	(b) (4)
Total (mg/tablet)								(b) (4)

(Source – Table 2, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

The effect of food on the PK of the tofacitinib MR formulation was evaluated in Study A3921131 (pilot formulation of MR 22 mg dose strength) and A3921180 (proposed commercial formulation of MR 11 mg dose strength) and is shown in Table 14.

T_{max} values were not appreciably altered with food. While coadministration of tofacitinib with meal had no impact on AUC_{inf} (90% CIs were contained within (80.00%-125.00%) in both studies), mean C_{max} was increased by 13% (MR 22 mg) and 27% (MR 11 mg) in A3921131 and A3921180, respectively. The magnitude of increase in C_{max} is not considered to be clinically relevant, therefore, no dose adjustments are recommended and tofacitinib can be administered without regard to meals.

Please refer to review by Office of New Drug Quality Assessment (ONDQA) reviewer for the effect of alcohol.

Table 14: Effect of Food on the PK of Tofacitinib MR Formulation (Studies A3921131 and A3921180)

PK Parameters	Adjusted Geometric Means		Statistical Comparison	
	Test (Fed)	Reference (Fasted)	Ratio (Test/Reference)[a]	90 % CI[a]
A3921131: Pilot Formulation (MR 22 mg)	**N=15**	**N=15**		
AUC_{inf} (ng·hr/mL)	739.1	737.5	100.22	94.86, 105.90
C_{max} (ng/mL)	112.0	99.02	113.09	99.54, 128.48
A3921180: Proposed-commercial Formulation (MR 11 mg)	**N=24**	**N=24**		
AUC_{inf} (ng·hr/mL)	268.6	265.6	101.11	96.94, 105.46
C_{max} (ng/mL)	47.09	37.02	127.21	116.57, 138.83

(Source – Table 30, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

No, there is only one strength (11 mg) of the to-be-marketed formulation.

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

The analytical methods used to measure tofacitinib in the pivotal PK study and other studies are summarized in Table 15. The bioanalytical methods used to measure tofacitinib in human plasma PK samples from the first two tofacitinib MR studies (A3921113 and A3921131) were developed and validated at (b) (4) under Pfizer validation report number A3929011. The bioanalytical method was then transferred to and validated at (b) (4) under Pfizer validation number A3929023.

Analytical method report # A3929023

Tofacitinib was extracted from human sodium heparinized plasma by 96-well solid phase extraction. Before the extraction, radiolabeled tofacitinib (i.e., [13C,15N] CP-690,550) was added as an internal standard. The samples were eluted with 13% ammonium hydroxide (NH4OH) in methanol, evaporated to dryness, and reconstituted with 50% methanol in water. The reconstituted sample was injected into an LC/MS/MS system using a Synergi Polar-RP column with a mobile phase of 0.03% formic acid and 4 mM ammonium acetate in 40% water and 60% methanol. The lower limit of quantitation (LLOQ) for tofacitinib in human plasma was 0.1 ng/mL, with linearity demonstrable to 350 ng/mL, using a sample volume of 50 µL (Table 16).

Table 15: Summary of Bioanalytical Methods Performance in Phase I Studies of Tofacitinib MR Clinical Development Program

Clinical Study	CP-690,550 Assay Performance	
	%RE[a]	%CV[a]
Analytical Method: A3929011; Laboratory:		(b) (4)
A3921113	-2.5 to 4.7	≤ 3.1
A3921131	-2.5 to 1.5	≤ 5.2
Samples Analytical Method: A3929023; Laboratory:		(b) (4)
A3921132	1.0 to 3.3	≤ 5.7
A3921163	1.3 to 4.7	≤ 4.6
A3921180	0.8 to 4.3	≤ 3.9
A3921195	0.5 to 3.3	≤ 4.7
A3921212	-0.4 to 5.7	≤ 9.1

%CV=percent coefficient of variation; %RE=percent relative error; MR=modified release.
[a] Statistics (%RE and %CV) based on mean assay performance of low, medium-low, medium-high, high and dilution (if applicable) Quality Control (QC) samples from all analytical batches meeting acceptance criteria.

Table 16: Summary of analytical method A3929023

Method Description	
Reference Standard(s)	CP-690550(CP-00690550-10), Lot 65806-24-5QS
Internal Standard	(b) (4) Lot 00116516-0151-KTG00A
Matrix	Human Plasma
Anticoagulant	Heparin Sodium
Source of Control Matrix	(b) (4)
Sample Storage Temperature	-20±5°C
Extraction Method	Solid Phase Extraction
Detection Method	HPLC-MS/MS
Sample Aliquot Volume	50 µL
Regression, Weighting	Quadraric, 1/conc.squared
Quantification	Peak Area Ratios
Calibration Range	0.100 to 350 ng/mL
ULOQ	350 ng/mL
LLOQ	0.100 ng/mL
Validation (VQC) Sample Concentrations	0.100, 0.300, 10.0, 280 and 700 (dilution VQC) ng/mL (From run 1 to run 8)
	0.100, 0.300, 4.00, 40.0, 280 and 700 (dilution VQC) ng/mL (From run 9 to run 19)

(Source – Table on Page 5, validation report A3929023)

2.9.2 Which metabolites have been selected for analysis and why?

No metabolites were measured in PK samples. Based on NDA203214, each of the metabolites in plasma had less than <8% of the total exposure. Sponsor also reported that potency of each metabolite was ≤10% of the parent drug.

2.9.3 For all moieties measured, is free, bound, or total measured?

Total (bound + unbound) concentrations were measured in plasma PK samples.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Details of the main bioanalytical methods are discussed in section 2.9.1.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

The standard curve for tofacitinib's analysis in plasma using method A3929023 ranged from 0.100 to 350 ng/mL. A quadratic regression model, with weighting factor of $1/concentration^2$ was used for the curve fitting for tofacitinib.

2.9.5.1 What are the lower and upper limits of quantitation?

LLOQ and ULOQ for A3929023 analytical method were 0.1 ng/mL and 350 ng/mL, respectively. For concentrations above 350 ng/mL, a 10-fold dilution factor was validated for 700 ng/mL concentration.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

The accuracy and precision of analytical method A3929023 are listed in Table 17. The imprecision for 10 fold dilution factor was less than 5%.

Table 17: Accuracy and Precision of Tofacitinib Analytical LC/MS/MS Assay (Validation Report # A3929023)

QC	Concentration (ng/mL)	Accuracy (%)		Precision (%)	
		Range of Intra-assay Daily Mean	Inter assay mean	Range of Intra-assay Daily Mean	Inter assay mean
LLOQ	0.1	-6.0 to 16.0	8.0	7.1 to 17.2	13.1
Low	0.3	-3.7 to 6.3	3.3	5.0 to 7.0	7.2
Medium	40	-0.8 to 3.8	3.5	1.4 to 2.0	4.3
High	280	-2.1 to 5.4	1.1	1.9 to 2.3	3.7

(Source – summarized based on Table 7 and Table 8, Validation report A3929023)

The selectivity was evaluated by extracting and analyzing blank human plasma from six individual sources both with and without addition of internal standard. All lots were free from significant interfering peaks in the drug and internal standard regions (Table 18).

Table 18: Selectivity of analytical method A3929023

Selectivity	
Matrix	6 out of 6 Human Heparin Sodium Plasma Lots Passed
Ionization Effects	6 out of 6 Human Heparin Sodium Plasma Lots Passed
Analyte Carryover	$\leq$ 17.9%
Internal Standard Carryover	$\leq$ 1.9%

(Source – Table on Page 6, validation report A3929023)

2.9.5.3 What is the sample stability under conditions used in the study?

The stability was demonstrated under different conditions as shown in Table 19:

Table 19: Summary of stability of analytical method A3929023

Stability	
Primary Stock Solution	22 hours at room temperature (15-30°C) 42 days at 2-8 °C
Ambient Temperature Matrix Stability	22 Hours at room temperature (15-30°C)
Freeze/Thaw Matrix Stability	5 Cycles at -20±5°C 5 Cycles at -80±10°C
Extract Stability	76 Hours at room temperature in 50: 50 MeOH: Water.
Re-injection Reproducibility Stability	74.5 Hours at room temperature in 50: 50 MeOH: Water.
Frozen Storage Matrix Stability	36 days at -20±5°C 31 days at -80±10°C 3, 6 and 12 months are on going

(Source – Table on Page 6, validation report A3929023)

3. DETAILED LABELING RECOMMENDATIONS

At this point, labeling negotiation is still ongoing. The initial labeling recommendations and comments were documented here.

Comment to sponsor:
"Please update the label to reflect the dose recommendations for the following situations:

- Patients with moderate to severe renal impairment;
- Patients with moderate hepatic impairment (tofacitinib is not recommended for patients with severe hepatic impairment);
- Co-administration with potent inhibitors of cytochrome P450 (CYP3A4) (e.g., ketoconazole, (b) (4) or;
- Co-administration with 1 or more medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

As tofacitinib IR 5 mg QD provided a much better PK profile and daily exposure (AUC) (b) (4) we recommend tofacitinib IR 5 mg QD for the above situations. "

4. APPENDIX

4.1 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA 208246
Submission Date	4/24/2015
Compound	Tofacitinib MR
Dosing regimen (route of administration)	11mg QD (oral administration)
Indication	RA
Clinical Division	DPARP
Primary PM Reviewer	Jianmeng Chen, M.D., Ph.D.
Secondary PM Reviewer	Yaning Wang, Ph.D.

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1.1. Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1. Will the difference in C_{min} affect the efficacy of tofacitinib MR?

The PK profile of the MR formulation, demonstrating overall similarity in PK parameters, with equivalent AUC and Cmax, and 29% lower Cmin compared to the approved IR dosing regimen. The observed data and application of PK/PD modeling approaches consistently showed that Cav appears to be the most relevant parameter for efficacy and that the 29% lower Cmin for the MR formulation may not be clinically important to the efficacy of tofacitinib.

The importance of C_{min} to the efficacy of tofacitinib was assessed using data from Study A3921025, a Phase 2B double-blind study of placebo and IR 1, 3, 5, 10, 15 mg BID and 20 mg QD doses of tofacitinib. Following administration of the same total daily dose in two different regimens (i.e. IR 20 mg QD or IR 10 mg BID), AUC24 was similar between the two regimens (within 10%), while C_{min} was approximately 7-fold (86%) lower and C_{max} was approximately 2-fold higher for the IR 20 mg QD dose compared to the IR 10 mg BID dose, respectively. Despite a large difference in C_{min}, the efficacy (measured by DAS28 improvements or American College of Rheumatology [ACR]20/50/70 responses at Week 12) of the IR 20 mg QD dose was similar to that of the IR 10 mg BID dose and consistent with the predicted BID dose response profiles across these endpoints (Figure 19 and Figure 20). The C_{min} difference observed in Study A3921025 is substantially larger than the 29% lower C_{min} observed for MR 11 mg QD compared to IR 5 mg BID in the MR program, supporting that this C_{min} difference is not clinically important to the efficacy of tofacitinib when there is equivalent AUC.

To characterize the most relevant tofacitinib PK parameter for efficacy and assess the predictive value of C_{min} over and above C_{av}, E-R analyses were conducted using DAS28

or ACR 20, 50, 70 responses at Week 12 from the pooled Phase 2 studies (A3921025, A3921035, A3921039, and A3921040) of the tofacitinib IR RA program. Comparison of the goodness of fit characteristics as measured by OFV or AIC for models with different PK parameters (C_{av} vs. C_{max} vs C_{min}) supported C_{av} as the most relevant PK parameter for efficacy. Furthermore, C_{min} did not provide additive predictive value over and above that of C_{av} in this analysis.

The totality of E-R evidence from the tofacitinib IR RA program, combined with demonstrated equivalence for AUC and C_{max} between the MR and IR formulations, support bridging of efficacy data derived using the IR 5 mg BID formulation to the MR 11 mg QD formulation.

1.1.2. What are the characteristics of the exposure-response relationship for safety?

All PK parameters for the MR 11 mg QD dose are equivalent (AUC and C_{max}) or slightly lower (29% lower C_{min}) as compared to those of the IR 5 mg BID dose. Benchmarking the expected tofacitinib exposures for MR 11 mg QD and IR 5 mg BID in RA patients against JAK inhibition, both doses cover the in-vitro JAK1/3 IC50 of 17 ng/mL for approximately 12 -13 hours over a 24-hour period, indicating a similar level of enzyme inhibition over the dosing interval (Figure 17).

The data from 20 mg IR QD in study 1025 suggested that the short term safety profile with once daily sustained inhibition of JAK1/3 for 12-13 hours is comparable to the BID dosing regimen. The dose response of short term safety profile was assessed for phase 2 clinical studies 1025, which is the only phase 2 study assessing efficacy and safety of once daily dosing with IR formulation. Short term safety of tofacitinib, as measured by laboratory parameters such as LDL, HDL, serum creatinine, and absolute neutrophil counts at 12 weeks, is dose dependent. A trend of decrease in neutrophil counts and increase in LDLC, HDLC, total cholesterol and serum creatinine was observed with increase in BID tofacitnib doses (1-15 mg BID) in study1025 (Figure 16, on background of MTX). However, the 20 mg QD dose appears to have better safety profiles as measured by these laboratory parameters, compared to 10 mg BID (Figure 16).

For the long term safety events, such as serious infection and malignancy, the AE information was all based on BID dosing regimens, and the PK parameters (C_{max}, C_{min} and C_{av}) were highly correlated. As the sponsor stated, the exposure response is consistent with dose response, and the tofacitnib concentration information did not provide additional explanation for the AEs. Please refer to review by clinical reviewer Dr. Juwaria Waheed for further details of safety evaluation.

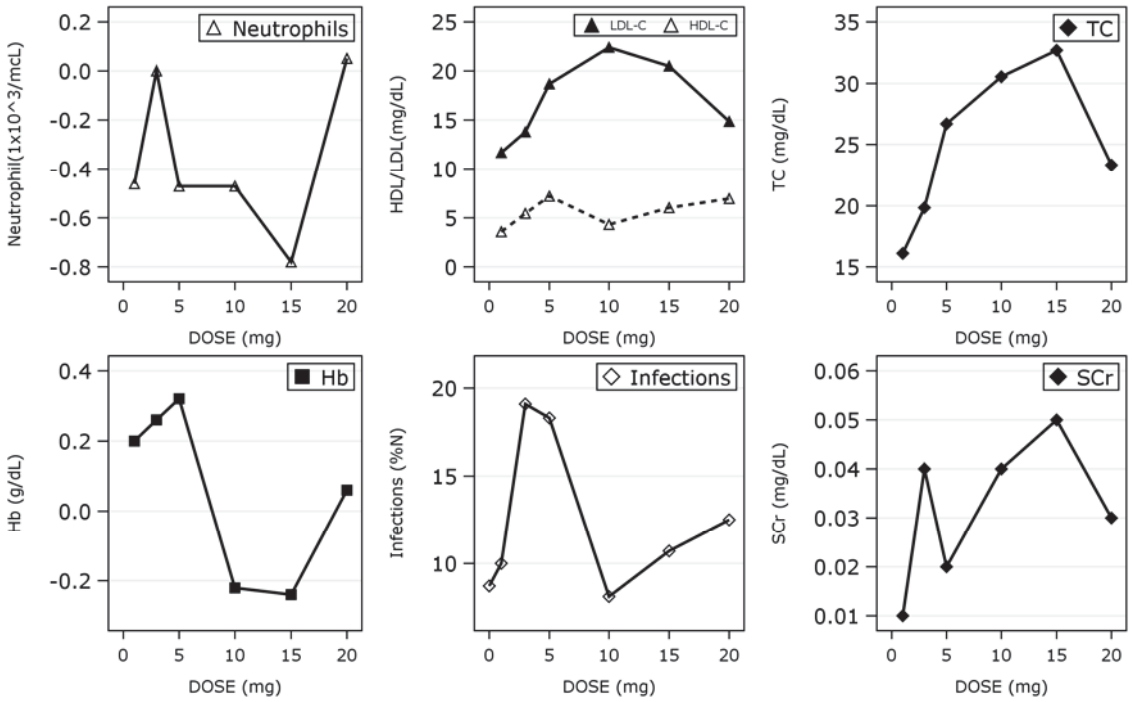


Figure 16: Dose-response relationship for safety endpoints from study 1025. Except infections all other endpoints are shown as placebo adjusted change from baseline to week 12 (delta baseline). Infections are reported as percent incidence at week 12. Except 20 mg QD all other doses were given in BID regimen (1, 3, 5, 10 and 15 mg BID).
(Source: Figure 19, NDA203214 Clin pharm review by Dr. Lokesh Jain)

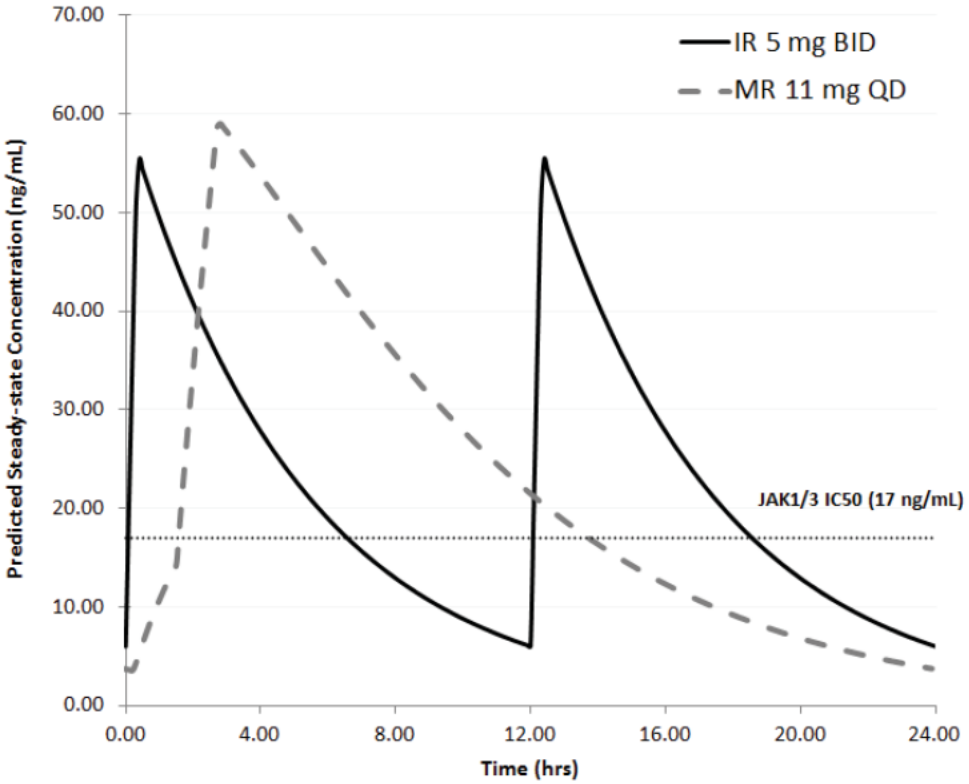


Figure 17. Predicted Steady State PK profiles in RA Patients Relative to JAK1/3 IC50

(Source: Figure 7, Summary Clin Pharm)

1.1.3. Is the dose and dosing regimen selected in special population supported by the Exposure- Response relationship?

The slower onset of efficacy relative to the daily fluctuations in PK plasma concentrations for tofacitinib suggests an indirect response relationship between drug PK and clinical effects on arthritic tissues.

While the sponsor suggested that the model (kinetic-pharmacodynamic model) predicted effective concentrations were comparable with the QD regimen [redacted]. As the alternative approach, tofacitinib IR 5 mg QD [redacted] recommend that tofacitinib IR 5 mg QD should be used in these populations.

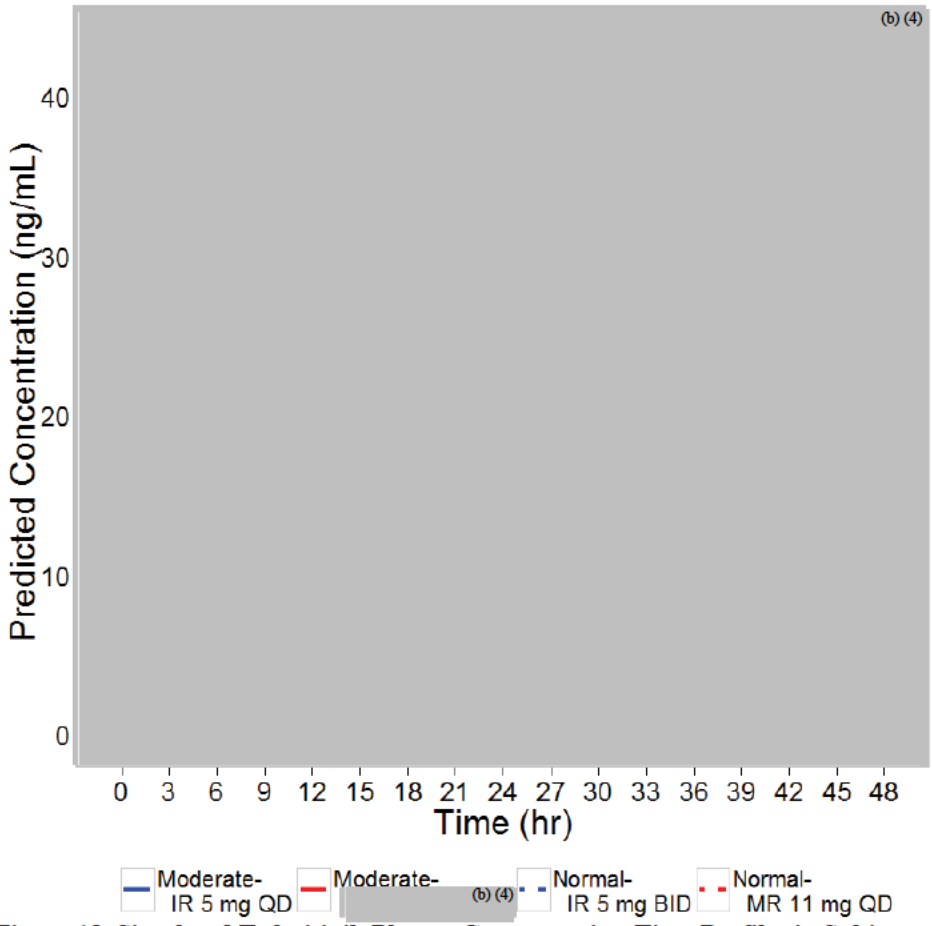


Figure 18. Simulated Tofacitinib Plasma Concentration-Time Profiles in Subjects with Normal Renal Function and Moderate Renal Impairment
(Source: Figure 9, Summary of clin pharm)

1.2. Recommendations

Considering the overall PK profile matching, we recommend that tofacitinib IR 5 mg QD should be used in the following populations. See section 1.1.3 and section 3.3.2 for further details.

- Patients with moderate to severe renal impairment;
- Patients with moderate hepatic impairment (tofacitinib is not recommended for patients with severe hepatic impairment);
- Co-administration with potent inhibitors of cytochrome P450 (CYP3A4) (e.g., ketoconazole, (b) (4) or;
- Co-administration with 1 or more medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

1.3. Label Statements

See Clinical pharmacology review section 3, Detailed Labeling Recommendations

2. PERTINENT REGULATORY BACKGROUND

Pfizer has developed an MR 11 mg osmotic tablet formulation of tofacitinib, to provide a QD dosing option to IR 5 mg BID. No new efficacy or safety studies have been conducted in RA patients using the tofacitinib MR formulation in support of this application. There have been several interactions between Agency and Sponsor to discuss the overall development program, including the exposure-response analysis to support the bridging of efficacy from IR formulation to MR formulation.

In the preNDA meeting in Dec 2014, FDA recommended that the PK/PD analysis use all relevant data including different dosing regimens (QD and BID). FDA also recommended PK/PD analysis for additional endpoints such as ACR20, ACR50, and ACR70 to justify that the difference in the trough concentrations would not translate into efficacy difference. The initial submission to NDA208246 did not include the QD regimen or ACR endpoints in the exposure-response analysis. An IR was sent to the sponsor, and the sponsor submitted the relevant information on Jul 29th, 2015.

In the 74 day letter, the review team communicated the potential review issue of dose recommendation (b) (4) Subsequently, the sponsor provided additional justification based on the PK/PD analysis on Oct 28th, 2015.

3. RESULTS OF SPONSOR'S ANALYSIS

The objectives of sponsor's Exposure-Response analysis were

• To support bridging efficacy from tofacitinib IR Formulation to MR Formulation

• To support bridging safety from tofacitinib IR Formulation to MR Formulation

• To support dose recommendation (b) (4) in patients whose previous dose recommendation is tofacitinib IR 5 mg QD.

3.1 Bridging Efficacy Data from Tofacitinib Immediate Release Formulation to Modified Release Formulation (Appendix 3 and 4, IR response 7/29/2015)

The objectives of the exposure-response analyses for efficacy were

- To develop an exposure-response (ER) model for tofacitinib, and describe dose-response from Study A3921025 data, which evaluated 1-15 mg twice daily (BID) and 20 mg once daily (QD) regimens of the immediate release (IR) formulation in rheumatoid arthritis (RA) patients.
- To develop an exposure-response (ER) model and identify the tofacitinib exposure metric that better predicts DAS28-3 C-reactive protein (CRP) response at Week 12.
- To develop an exposure-response (ER) model and identify which of the evaluated tofacitinib exposure metrics best predicts the ACR20, ACR50 and ACR70 responses at Week 12.

3.1.1 Methods

Data

Pooled data from four double-blind Phase 2 studies (A3921025, A3921035, A3921039, A3921040), at Week 12 comprising placebo and IR 1, 3, 5, 10 and 15 mg twice daily (BID), and 20 mg once daily (QD), were used to support models estimating the exposure-

response (E-R) relationships. Data from 964 patients, who received placebo or tofacitinib, were available for this analysis. The models incorporated data for the ordered categorical responses for ACR20, ACR50 and ACR70 together with subject-specific predictions of three exposure metrics including: average (C_{av}, the area under the concentration-time curve divided by the dosing interval), minimum (C_{min}) and maximum (C_{max}) tofacitinib plasma concentrations at steady-state predicted from the population pharmacokinetics (popPK) model (PMAR-00178, NDA 203214).

Model Development

Emax models for ACR or DAS 28 response at Week 12 were compared to assess the predictive ability of different tofacitinib exposure metrics. The tested exposure metrics were individual predicted C_{av}, C_{min} and C_{max} tofacitinib concentrations at steady-state. The data from a total of 964 patients were available for ACR E-R analysis, and 969 patients were available for DAS 28 E-R analysis..

The three ACR endpoints were jointly modeled by forming a 4-category response model (ACR20 non-responder, ACR20 but not ACR50 responder, ACR50 but not ACR70 responder, and ACR70 responder) represented by values of 0, 1, 2, and 3 respectively. The general form of the ACR model was given by the expression:

$$logit\left(Pr\left(ACR_{ij} \geq m\right)\right) = \beta_{1j} - \sum_{k=2}^{m} e^{\beta_{kj}} + \frac{E_{\max,j} C_{ij}}{EC_{50} + C_{ij}}$$

Where the probabilities that ACR ≥ m (m=1, 2 or 3) are modeled on the logit scale, i.e., logit(p) = log(p) – log(1-p); β1j is the baseline logit probability that ACR ≥ 1 for study j (j corresponds to Studies 1025, 1035, 1039, and 1040, respectively); β 1j – exp(β 2j) is the baseline logit probability that ACR ≥ 2; β 1j – exp(β 2j) – exp(β 3j) is the baseline logit probability that ACR=3; Cij is the steady-state tofacitinib concentration (C_{av}, C_{min} or C_{max} depending on the model) for the i-th subject in study j; Emax,j is the maximum drug effect in the logit scale for study j; and EC50 is the steady-state tofacitinib concentration corresponding to 50% of the maximum drug effect. Sharing the EC50 and Emax parameters across the ordered categorical responses facilitates more efficient estimation of these parameters. Goodness-of-fit plots were used to evaluate the adequacy of this assumption.

DAS28 is a composite endpoint composed of several subjective endpoints. The structural model form evaluated was based on an Emax model:

$$DAS28\ (time = 12\ week) = DAS28_{Placebo} + \frac{Emax \times Exposure}{EC_{50} + Exposure}$$

Where DAS28 is DAS28-3 (CRP); Exposure is either C_{av}, C_{min} or C_{max}.

Different PK parameters (C_{av}, C_{min} or C_{max}) were fit to the model as exposure metrics, or as covariate of Emax or EC50, and were then compared based on Objective function value (OFV), and Akaike information criterion (AIC [2]) with a per-parameter (k) penalty of 2:

$(AIC = 2 \times k + OFV)$

For E-R analysis of ACR endpoints, the models were fit using maximum likelihood estimation as implemented in the NLMIXED procedure in SAS Version 9.3. For E-R analysis of DAS28, the models were fit using the NONMEM version 7.1.2.

3.1.2 Results

Exploratory Data Analysis of Dose response in study A3921025

In a first step, an exploratory analysis was evaluated using graphical tools, assessing the dose response on DAS28 and ACR response rates (ACR20/50/70) from Study A3921025 to examine the consistency of IR 20 mg QD responses relative to the BID dose response profiles.

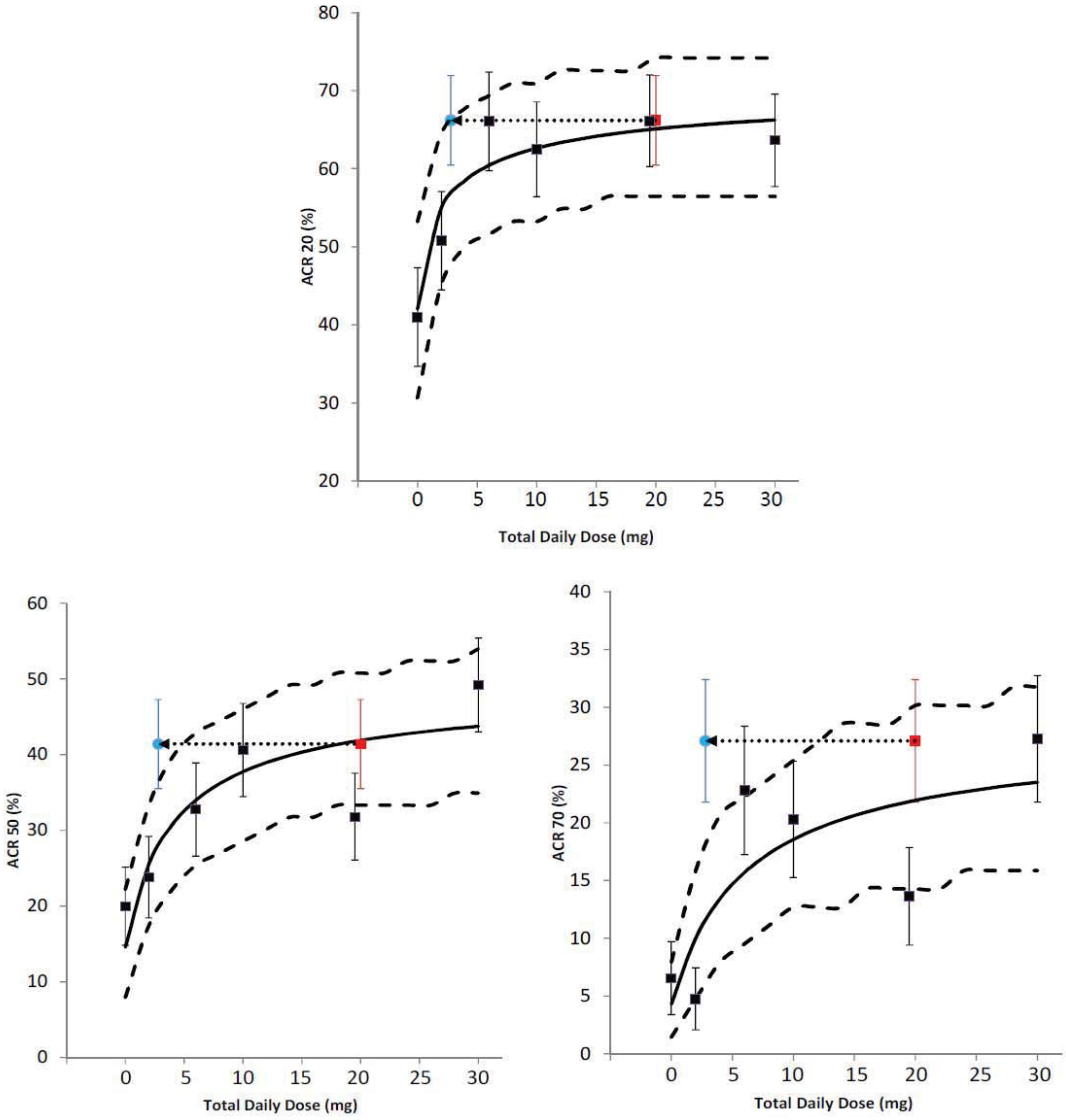
Figure 19 displays the observed and model-predicted ACR responses for BID doses at Week 12, overlaid with the observed response rates for IR 20 mg QD. To assess whether efficacy is consistent with AUC or C_{min}, the IR 20 mg QD response data are displayed at two different locations; one corresponding to a total daily dose of 20 mg (red square in the figure) since AUC_{24} is proportional to total daily dose across QD and BID regimens, and the other corresponding to a total daily dose of 2.8 mg (blue circle) to reflect the approximately 7-fold (86%) lower C_{min} for IR 20 g QD compared to IR 10 mg BID. As shown in Figure 19, the red squares are well within the prediction intervals of the BID dose response curve on all 3 measures (ACR20/50/70) and consistent with AUC24 as the driver. On the other hand, the blue circles are higher than would be predicted from the BID curves, indicating that C_{min} is not a driver of efficacy.

Similar assessment was done for DAS28 response. DAS28 scores and DAS28 change from baseline at Week 12 for the same total daily dose administered QD or BID, showed similar responses for IR20 mg QD(DAS28 mean[SE] change from baseline -1.72 [0.14]) and IR 10 mg BID (-1.82 [0.15]). To assess whether efficacy is consistent with AUC or C_{min}, the IR 20 mg QD response data are displayed at two different locations; one corresponding to a total daily dose of 20 mg (red square in the figure) since AUC_{24} is proportional to total daily dose across QD and BID regimens, and the other corresponding to a total daily dose of 2.8 mg (blue circle) to reflect the approximately 7-fold (86%) lower C_{min} for IR 20 g QD compared to IR 10 mg BID. As shown in Figure 20, the red squares is close to the prediction intervals of the BID dose response curve for DAS28 and consistent with AUC24 as the driver. On the other hand, the blue circles are lower than would be predicted from the BID curves.

Table 20. Summary of observed and predicted C_{min} for Study A3921025

	20 mg qd	1 mg bid	3 mg bid	5 mg bid	10 mg bid	15 mg bid
Predose observed (ng/mL)	2.06 (n=49)	0.95 (n=42)	4.81 (n=42)	4.96 (n=42)	11.07 (n=44)	11.46 (n=47)
C_{min} Predicted (ng/mL)	0.29 (n=80)	0.65 (n=72)	2.32 (n=68)	3.56 (n=71)	7.75 (n=79)	10.41 (n=79)

(Source: Reviewer summary, Table 17, Table 12, PMAR-00178 pop PK report, NDA203214)



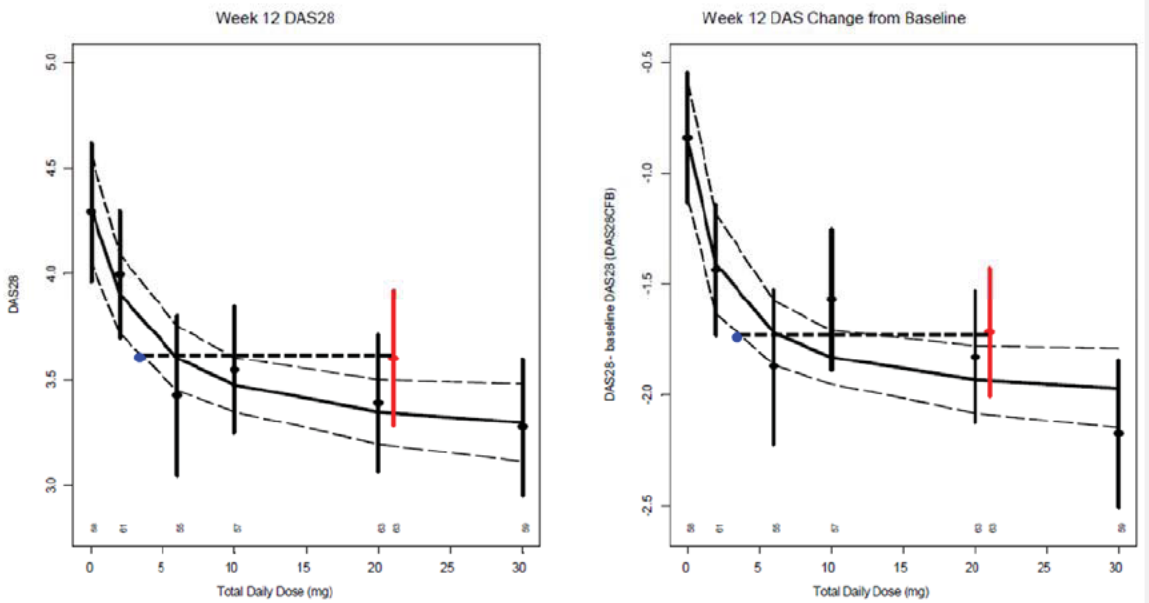
The observed proportion of ACR20/50/70 responders for IR 20 mg QD dose at Week 12 is overlaid with model-predicted posterior mean (10^{th}-90^{th} percentiles) from a longitudinal E_{max} model applied to BID doses in Study A3921025. Doses are presented on a total daily dose scale.

Black solid line represents posterior mean model prediction, black dashed line represents 80% prediction intervals from the model; black filled squares represent observed data for BID doses; red filled square and blue filled circle represent 20 mg QD data placed either at a x-axis value of 20 (reflecting the same AUC_{24} as 10 mg BID) or at a x-axis value of 2.8 (reflecting the 86% lower C_{min} compared to 10 mg BID), respectively; error bars on filled squares and filled circle represent standard error. Black dotted arrow facilitates comparison of responses based on AUC_{24} and C_{min} values for 20 mg QD regimen.

%=percentage of responders; ACR=American College of Rheumatology; AUC_{24}=area under the concentration-time profile from time 0 to 24 hours; BID=twice daily; C_{min}=minimum plasma concentration; E_{max}=maximum drug effect; IR=immediate release; mg=milligrams; QD=once daily.

Figure 19. Observed and Posterior Predicted Mean (10th-90th Percentile) Proportion of ACR20/50/70 Responders at Week 12 (Study A3921025)

(Source: Figure 4, Summary of Clin Pharm)



The 95% CI for the efficacy endpoints of the IR 20 mg QD dose relative to placebo and IR BID doses is overlaid with model-predicted 95% CI band for DAS28 response at Week 12. Doses are presented on a total daily dose scale.
Black solid line represents typical model prediction, black dotted line represents 95% CI of the model prediction; red filled circle represents 20 mg QD data; black filled circles represents BID data; error bars on filled circles represent empirical 95% CIs. The numbers above the x-axis inside the plots represent the number of patients at each dose level. DAS28CFB represents difference of DAS28 at Week 12 and baseline DAS28.
CFB=change from baseline; CI=confidence interval; DAS=disease activity score; IR=immediate release; mg=milligrams; Pred= typical model prediction; QD=once daily; RA=rheumatoid arthritis.

Figure 20. Dose-Response Relationship of DAS28 at Week 12 in RA Patients Receiving Tofacitinib Twice Daily Using IR Tablets (Study A3921025)
(Source: Figure 3, Summary of Clin Pharm)

The C_{min} difference observed in the study is substantially larger than the 29% lower C_{min} observed for MR 11 mg QD compared to IR 5 mg BID. Thus, this C_{min} difference is not considered clinically important to the efficacy of tofacitinib given the equivalent C_{max} and AUC between the two formulations.

Exposure response model of ACR

$$logit\left(Pr\left(ACR_{ij} \geq m\right)\right) = \beta_{1j} - \sum_{k=2}^{m} e^{\beta_{kj}} + \frac{E_{\max,j} C_{ij}}{EC_{50} + C_{ij}}$$

Table 21 summarizes the model evaluation criteria for the different E-R models, and Table 22 summarizes the parameter estimates for different exposure matrices. The Emax model using C_{av} as the exposure metric without covariate (AVG) was the best predictor of the ACR response at Week 12, which is demonstrated by the lowest AIC value (2371.987). The three analysis stages support that C_{av} better predicts ACR response at Week 12 when compared to C_{min} or C_{max}.

- Stage 1: The model using C_{av} as the univariate exposure metric had the lowest AIC value.

- Stage 2: The inclusion of C_{min} as a covariate on Emax or EC50 in the model using C_{av} as the primary exposure metric did not yield a significant improvement.
- Stage 3 (sensitivity analysis): The inclusion of C_{av} as a covariate on Emax or EC50 in the model using C_{min} as the primary exposure metric yielded a significant improvement.

Table 21. Summary of Exposure-Response Models for ACR at Week 12

Model ID	Exposure metric as independent variable	Exposure metric as covariate	Number of parameters	OFV	AIC
First Stage					
AVG (Run 1)	C_{av}	None	17	2337.987	2371.987
MAX (Run 2)	C_{max}	None	17	2340.001	2374.001
MIN (Run 3)	C_{min}	None	17	2365.066	2399.066
Second Stage					
AVG-1 (Run 4)	C_{av}	C_{min} as covariate of EC_{50}	18	2337.986	2373.986
AVG-2 (Run 5)	C_{av}	C_{min} as covariate of E_{max}	18	2337.908	2373.908
Third Stage (Sensitivity Analysis)					
MIN-1 (Run 6)	C_{min}	C_{av} as covariate of EC_{50}	18	2354.001	2390.001
MIN-2 Run 7)	C_{min}	C_{av} as covariate of E_{max}	18	2357.041	2393.041

Total number of patients is 964. ID is identification. OFV is the minimum value of −2×log-likelihood. AIC is the Akaike information criterion with a per parameter penalty of 2 (2×k+OFV), where k is the number of parameters.

(Source: Table 1, Summary Report of ACR Exposure-Response Analysis)

Table 22. Summary of Parameter Estimates from ACR Exposure-Response Models

Model ID / Parameter (90% CI)	AVG	AVG-1	AVG-2	MIN	MIN-1	MIN-2
$\theta_{Covariate}$	NA	0.003 (-0.051, 0.056)	-0.002 (-0.009, 0.013)	NA	-0.0391 (-0.0438, -0.0344)	0.00957 (0.00220, 0.0169)
θ_{EC50} (ng/mL)	12.7 (6.84, 18.6)	13.0 (5.86, 20.2)	11.9 (4.74, 19.1)	2.13 (1.06, 3.20)	1.02 (0.593, 1.44)	0.500 (-0.221, 1.22)
θ_{Emax} Prot 1025	1.51 (0.965, 2.06)	1.52 (0.917, 2.13)	1.47 (0.886, 2.06)	0.744 (0.261, 1.23)	0.859 (0.468, 1.25)	0.670 (0.313, 1.03)
θ_{Emax} Prot 1035	2.86 (1.91, 3.81)	2.89 (1.82, 3.97)	2.78 (1.72, 3.85)	2.57 (1.69, 3.45)	2.09 (1.42, 2.77)	1.69 (1.00, 2.38)
θ_{Emax} Prot 1039	4.99 (3.65, 6.32)	5.03 (3.47, 6.60)	4.87 (3.40, 6.33)	4.44 (3.23, 5.64)	3.77 (2.75, 4.78)	3.42 (2.28, 4.55)
θ_{Emax} Prot 1040	4.89 (4.04, 5.74)	4.93 (3.84, 6.02)	4.77 (3.68, 5.85)	4.53 (3.74, 5.32)	3.62 (2.97, 4.26)	3.00 (2.03, 3.98)

CI is a Wald-based confidence interval derived from approximate standard errors. Prot is the study protocol. E_{max} is the maximum drug effect. EC_{50} is the drug concentration producing 50% of E_{max}. ID is the identification number. NA denotes not applicable.

(Source: Table 2, Summary Report of ACR Exposure-Response Analysis)

Exposure response model of DAS 28

DAS28 is a composite endpoint composed of several subjective endpoints. The structural model form evaluated was based on an Emax model:

$$DAS28\,(time = 12\ week) = DAS28_{Placebo} + \frac{Emax \times Exposure}{EC_{50} + Exposure}$$

Table 23 summarizes the model evaluation criteria for the different E-R models, and Table 24 summarizes the parameter estimates for different exposure matrices. The Emax model using C_{av} as the exposure metric without covariate (AVG) was the best predictor of the DAS28-3 (CRP) response at Week 12 as demonstrated by the lowest AIC value (1286.557). The three analysis stages support that C_{av} better predicts DAS28-3 (CRP) at Week 12 when compared to C_{min} or C_{max}.

- Stage 1: The model using C_{av} as the univariate exposure metric had the lowest AIC value.
- Stage 2: The inclusion of C_{min} as a covariate on Emax or EC50 in the model using C_{av} as the primary exposure metric did not yield a significant improvement.
- Stage 3 (sensitivity analysis): The inclusion of C_{av} as a covariate on EC50 in the model using C_{min} as the primary exposure metric yielded a significant improvement.

Table 23. Summary of Exposure-Response Models for DAS28-3(CRP) at Week 12

Model ID	Exposure metric as independent variable	Exposure metric as covariate	Number of parameters	OFV	AIC
First Stage					
AVG (Run 1)	C_{av}	None	8	1270.557	1286.557
MAX (Run 2)	C_{max}	None	8	1278.381	1294.381
MIN (Run 3)	C_{min}	None	8	1283.139	1299.139
Second Stage					
AVG-1 (Run 4)	C_{av}	C_{min} as covariate of EC_{50}	9	1270.436	1288.436
AVG-2 (Run 5)	C_{av}	C_{min} as covariate of E_{max}	9	1270.548	1288.548
Third Stage (Sensitivity Analysis)					
MIN-1 (Run 6)	C_{min}	C_{av} as covariate of EC_{50}	9	1277.499	1295.499
MIN-2 (Run 7)	C_{min}	C_{av} as covariate of E_{max}	9	1281.045	1299.045

Total number of patients is 969. ID is identification. OFV is the minimum value of the NONMEM objective function. AIC is the Akaike information criterion with a per parameter penalty of 2 (2×k+OFV), where k is the number of fixed effects parameters.

(Source: Table 1, Appendix 4a, Summary clin pharm)

Table 24. Summary of Parameter Estimates from DAS28 Exposure-Response Models

Model ID / Parameter (90% CI)	AVG	AVG-1	AVG-2	MIN	MIN-1	MIN-2
$\theta_{Covariate}$	NA	-0.0109 (-0.0570, 0.0352)	-0.0006 (-0.0123, 0.0112)	NA	-0.0240 (-0.0309, -0.0172)	0.00582 (-0.00321, 0.0128)
θ_{EC50} (ng/mL)	13.6 (8.89, 20.9)	12.7 (7.65, 21.1)	13.9 (7.47, 26.0)	2.31 (1.52, 3.52)	1.57 (1.02, 2.42)	1.18 (0.308, 4.55)
θ_{Emax} Prot 1025	-1.09 (-1.44, -0.730)	-1.05 (-1.43, -0.679)	-1.10 (-1.49, -0.706)	-0.808 (-1.14, -0.472)	-0.766 (-1.06, -0.475)	-0.686 (-0.982, -0.390)
θ_{Emax} Prot 1035	-2.07 (-2.46, -1.68)	-2.00 (-2.45, -1.56)	-2.09 (-2.64, -1.53)	-1.93 (-2.30, -1.55)	-1.62 (-1.93, -1.30)	-1.52 (-2.14, -0.892)
θ_{Emax} Prot 1039	-2.43 (-3.04, -1.82)	-2.35 (-3.03, -1.66)	-2.45 (-3.23, -1.67)	-2.22 (-2.78, -1.67)	-1.94 (-2.42, -1.46)	-1.83 (-2.50, -1.16)
θ_{Emax} Prot 1040	-2.99 (-3.36, -2.61)	-2.89 (-3.38, -2.40)	-3.01 (-3.71, -2.32)	-2.85 (-3.18, -2.51)	-2.39 (-2.66, -2.12)	-2.21 (-3.09, -1.33)

CI is a Wald-based confidence interval derived from the NONMEM approximate standard errors. Prot is study protocol. E_{max} is maximum drug effect. EC_{50} is drug concentration producing 50% of E_{max}. ID is identification. NA is not applicable.

(Source: Table 2, Appendix 4a, Summary clin pharm)

Conclusion:
The exposure-response analysis supports C_{av} as the more relevant PK parameter for efficacy, with little additional predictive value of C_{min} over and above C_{av}.

Reviewer's comments: *A rigorous analysis assessing the relevant PK parameter for tofacitinib efficacy was performed using Emax model, with the primary endpoint ACR 20 and other endpoints such as DAS 28, ACR 50 and 70. Goodness-of-fit plots based on the sponsor's analyses showed that the model fitted the data reasonably well. Also, the reviewer's independent analysis of ACR 20 resulted in similar results that* C_{av} *is the most relevant PK parameter. Overall, the reviewer concludes that the analysis, and the corresponding conclusions and interpretations, presented by the sponsor are reasonable.*

3.2 Bridging Safety Data from Tofacitinib Immediate Release Formulation to Modified Release Formulation

All PK parameters for the MR 11 mg QD dose are equivalent (AUC and C_{max}) or slightly lower (29% lower C_{min}) as compared to those of the IR 5 mg BID dose. Benchmarking the expected tofacitinib exposures for MR 11 mg QD and IR 5 mg BID in RA patients against JAK inhibition, both doses cover the in-vitro JAK1/3 IC50 of 17 ng/mL for approximately 12 -13 hours over a 24-hour period, indicating a similar level of enzyme inhibition over the dosing interval (Figure 21).

Quantitative characterization of E-R relationships with tofacitinib IR formulation for several safety outcomes including serious infections and malignancies was reported in PMAR-00188 in NDA203214. For serious infection, both dose and concentration-based exposure metrics suggested that there is an exposure-dependent increase in the risk of these infections. The precision of the E-R relationships indicated that C_{max} or C_{min} did not provide additional predictive value over and above dose or AUC. No apparent association between any tofacitinib exposure parameter and malignancy risk could be identified from linear logistic analysis. Similar results were obtained from the E-R analyses of a number of additional parameters such as lymphocyte subsets, hemoglobin, LDL, neutrophils, creatinine, ALT, and other AEs.

Overall, based on the PK profile of the tofacitinib MR formulation and knowledge of the exposure-safety relationship from the tofacitinib IR program, the overall safety profile is expected to be consistent with that of the IR formulation.

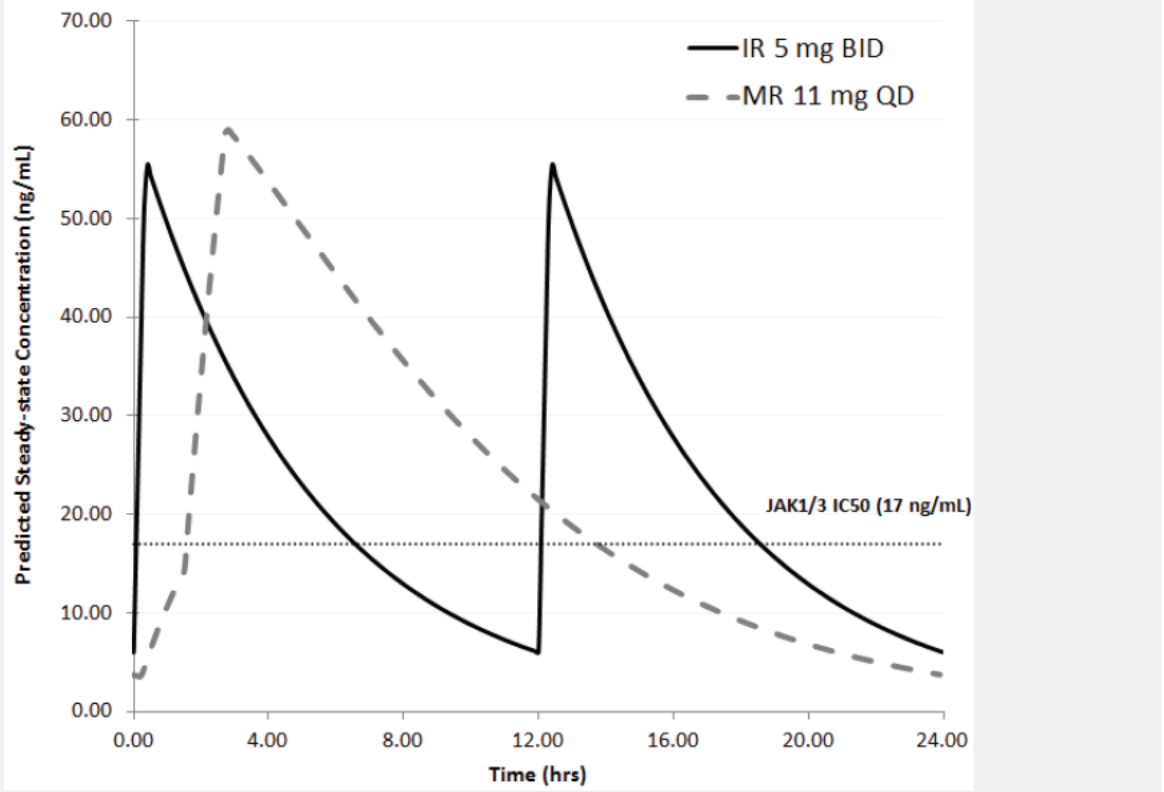


Figure 21. Predicted Steady State PK profiles in RA Patients Relative to JAK1/3 IC50

(Source: Figure 7, Summary Clin Pharm)

Reviewer's comments: *The exposure response for safety was reviewed for tofacitinib IR formulation in NDA203214. As the sponsor stated, the exposure response is consistent with dose response, and the tofacitnib concentration information did not provide additional explanation for the AEs. For the long term safety events, such as serious infection and malignancy, the AE information was all based on BID dosing regimens, and the PK parameters (C_{max}, C_{min} and C_{av}) were highly correlated. Therefore, we cannot identify the most relevant PK parameter for these AEs.*

For short term safety measured by laboratory parameters, such as LDL, HDL, serum creatinine, and absolute neutrophil counts, the 20 mg QD dose appears to have better safety profiles as measured by these laboratory parameters, compared to 10 mg BID (Figure 22, study 1025). The data from 20 mg IR QD in study 1025 suggested that the short term safety profile with once daily sustained inhibition of JAK1/3 for 12-13 hours is comparable to the BID dosing regimen. Please refer to review by clinical reviewer Dr. Juwaria Waheed for further details of safety evaluation.

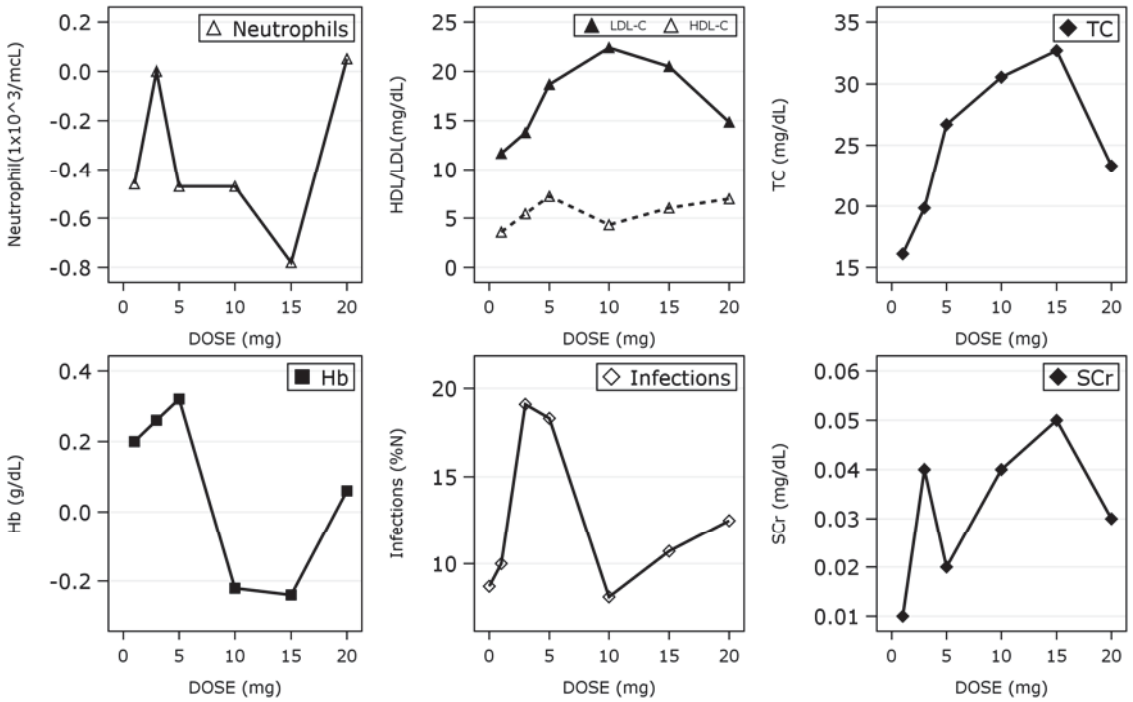


Figure 22: Dose-response relationship for safety endpoints from study 1025. Except infections all other endpoints are shown as placebo adjusted change from baseline to week 12 (delta baseline). Infections are reported as percent incidence at week 12. Except 20 mg QD all other doses were given in BID regimen (1, 3, 5, 10 and 15 mg BID).
(Source: Figure 19, NDA203214 Clin pharm review by Dr. Lokesh Jain)

3.3 Characterization of Delay in Time Course of Efficacy Response and Dose Recommendation for Special Population (Appendix 1, Appendix 2, 10/28/2015 IR response)

3.3.1. Methods

Data

This ER analysis was based on the clinical studies with tofacitinib IR BID (Table 25). Observed Disease Activity Score (DAS)28-3(C-reactive protein [CRP]) data (referred to as DAS28 below) were analyzed; no imputations were used. Table 25 and Table 26 display the number of subjects and the number of observations, respectively, contributing to the analysis by study and randomized dose amount from the IR BID program.

Table 25. Numbers of Subjects by Study and Randomized Dose

Randomized Dose	Study					Total
Dose (mg)	A3921019	A3921025	A3921035	A3921039	A3921040	
0	51	67	58	28	52	256
1	0	65	54	28	53	200
3	0	65	51	27	53	196
5	50	69	47	27	52	245
10	0	73	59	26	53	211
15	57	75	57	0	54	243

(Source: Table 1, appendix 2, summary clin pharm)

Table 26. Numbers of Observations by Study and Randomized Dose

Randomized Dose	Study					Total
Dose (mg)	A3921019	A3921025	A3921035	A3921039	A3921040	
0	221	510	470	153	250	1604
1	0	519	464	159	259	1401
3	0	507	471	152	251	1381
5	238	510	438	157	251	1594
10	0	560	542	143	255	1500
15	272	563	518	0	262	1615

(Source: Table 2, appendix 2, summary clin pharm)

Model Development

The structural model form evaluated was based on an Emax model:

$$DAS28^{*} = DAS28 - 0.96 = exp\left(Base + Placebo(t) + \frac{Emax \cdot E(t)}{E(t) + ED50}\right) + \varepsilon$$

Where Base represents a baseline function of parameters, Placebo(t) represents the non-drug function of parameters. During model development, Onset of drug effect or hysteresis was evaluated first by using an effective exposure model (effect-site like). Additionally, study-specific parameters were included to adjust for differences across studies and to facilitate pooling. The final model can be described as:

$$DAS28^{*} = exp\left(Base + Pmax\left[1 - \frac{\ln 2}{exp(Pthalf)}t\right] + \frac{Emax \cdot E(t)}{E(t) + ED50}\right) + g \cdot \varepsilon$$

$$Base = \theta_1 + \theta_8 I_{1019} + \theta_9 I_{1039,1040} + \eta_1$$

$$Pmax = \theta_2 + \theta_{23} I_{1040} + \eta_2$$

$$Pthalf = exp(\theta_3 + \theta_{20} I_{1019} + \theta_{21} I_{1039,1040} + \theta_{22} I_{1040})$$

$$Emax = \theta_4 + \theta_{10} I_{1019} + \theta_{11} I_{1039,1040} + \eta_3$$

$$ED50 = exp(\theta_5)$$

$$E(t) = \begin{cases} D_1[1 - exp(-keo \cdot t)] & t \le T_{SW} \\ D_1[1 - exp(-keo \cdot T_{SW})]exp(-keo \cdot [t - T_{SW}]) + D_2[1 - exp(-keo \cdot [t - T_{SW}])] & t > T_{SW} \end{cases}$$

$$keo = \frac{\ln 2}{exp(Kthalf)} = \frac{\ln 2}{exp\left(\theta_7 + \frac{KEmax \cdot D(t)}{ED50 \cdot KED50F + D(t)}\right)}, where\ D(t) = \begin{cases} D_1 & t \le T_{SW} \\ D_2 & t > T_{SW} \end{cases}$$

$$KEmax = \theta_{24}$$

$$KED50F = exp(\theta_{25})$$

$$g = exp(\theta_6 + \theta_{18} I_{1019} + \theta_{19} I_{1039,1040})$$

$$\eta \sim N(0, \Omega);\ \varepsilon \sim N(0,1)$$

3.3.2 Results

Time course of Change from Baseline in DAS Components (Appendix 1, Study A3921019)

The onset and offset of pharmacodynamic effects of tofacitinib in rheumatoid arthritis patients were assessed in the dose-ranging study A3921019. RA patients who had an inadequate response to methotrexate were randomized to receive IR 5, 15 or 30 mg BID as monotherapy or placebo for 6 weeks and changes in DAS28 were evaluated during treatment and at 2 weeks after cessation of treatment.

Changes in C-reactive protein (CRP) and DAS28-3 (CRP) scores observed with CP-690,550 treatment continued to show residual activity for at least 2 weeks after cessation of treatment (Figure 23), indicating prolonged pharmacodynamic residual activity compared to short PK half-life of ~3 hrs.

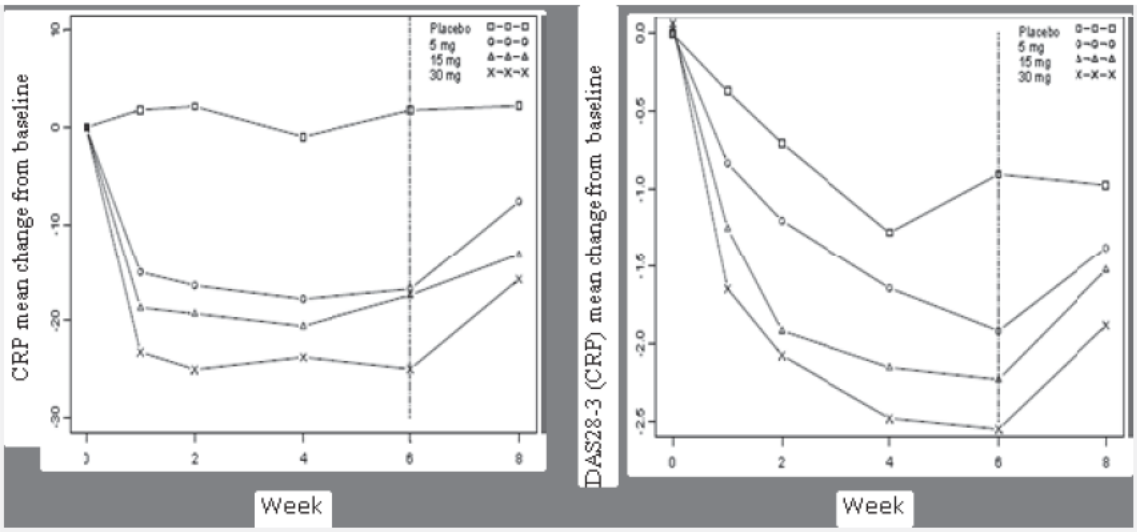


Figure 23: Time Course of Changes in CRP and DAS28-3(CRP) in Study A3921019

(Source: Figure 2, study-pmar-00223 report/page 12)

Development of a longitudinal exposure-response (ER) model to predict effective concentration-time profiles for IR twice daily (BID) and MR once daily (QD) formulations in RA patients (Appendix 1, Study A3921019)

The parameter estimates for the final model are displayed below in Table 27. The typical individual is predicted to have a baseline DAS28 response of 4.35 units. The maximum placebo effect is estimated to be a 31.1% decrease relative to baseline DAS28 responses (multiplicative factor of 0.689). The onset half-life of the placebo effect (Pthalf) was estimated to be slow at 8.51 weeks; however, the half-lives for studies 1019 and 1039 were estimated to be faster than this (nearly 25% shorter half-life). These estimated results are likely due to the small effect size or flatness of the placebo effect. The estimate of the Emax translates to a maximum 54.6% reduction in DAS28 relative to that of placebo. The minimum onset half-life (Kthalf) is 1.04 weeks (at very low doses), while the maximum onset half-life is 9.3-fold longer (at higher doses).

Table 27. Parameter Estimates for the Population DAS28 Final Model

Parm	THETA	Original Units	Original Estimate	ASE	Transformed Estimate	Transformed 90% CI	Transformed Units
BASE	1	Log(DAS28)	1.47	0.00825	4.35	(4.29,4.41)	DAS28
BASE 1019	8	Log(DAS28)	0.107	0.0166	1.11	(1.08,1.14)	Frac
BASE 1039,1040	9	Log(DAS28)	-0.072	0.0129	0.931	(0.911,0.951)	Frac
PMAX	2	Log(DAS28)	-0.372	0.0338	0.689	(0.652,0.729)	Frac
PMAX 1040	23	Log(DAS28)	0.145	0.0588	1.16	(1.05,1.27)	Frac
Pthalf	3	Log(Weeks)	2.14	0.0981	8.51	(7.24,10)	Weeks
Pthalf 1019	20	Log(Frac)	-0.566	0.211	0.568	(0.401,0.803)	Frac
Pthalf 1039,1040	21	Log(Frac)	-0.283	0.158	0.753	(0.581,0.977)	Frac
Pthalf 1040	22	Log(Frac)	0.479	0.191	1.61	(1.18,2.21)	Frac
EMAX	4	Log(DAS28)	-0.790	0.0578	0.454	(0.413,0.499)	Frac
EMAX 1019	10	Log(DAS28)	-0.144	0.0822	0.866	(0.756,0.991)	Frac
EMAX 1039,1040	11	Log(DAS28)	-0.600	0.082	0.549	(0.479,0.628)	Frac
LOG(ED50)	5	Log(mg)	1.52	0.143	4.55	(3.60,5.77)	mg
LOG(Kthalf)	7	Log(Weeks)	0.0399	0.288	1.04	(0.648,1.67)	Weeks
KEMAX	24	Log(Frac)	2.23	0.264	9.30	(6.02,14.4)	Frac
KED50F	25	Log(Frac)	0.0257	0.361	1.03	(0.566,1.86)	Frac
ETA1	12	--	-1.69	0.0264	0.185	(0.177,0.193)	CV
COV(1,2)	13	--	-0.0513	0.0285	-0.0833	(-0.158,-0.00689)	rho
ETA2	14	--	-0.489	0.0542	0.615	(0.565,0.674)	CV
COV(1,3)	15	--	0.183	0.0401	0.223	(0.142,0.302)	rho
COV(2,3)	16	--	-0.383	0.0592	-0.485	(-0.561,-0.392)	rho
ETA3	17	--	-0.356	0.0593	0.819	(0.736,0.911)	CV
LOG(W)	6	Log(DAS28)	-0.538	0.011	0.584	(0.573,0.594)	DAS28
g 1019	18	Log(DAS28)	-0.0971	0.033	0.907	(0.860,0.958)	Frac
g 1039,1040	19	Log(DAS28)	-0.223	0.0235	0.800	(0.770,0.831)	Frac

ASE = approximate standard error; CV = coefficient of variation; Frac = fraction; rho = correlation; Parm = parameter

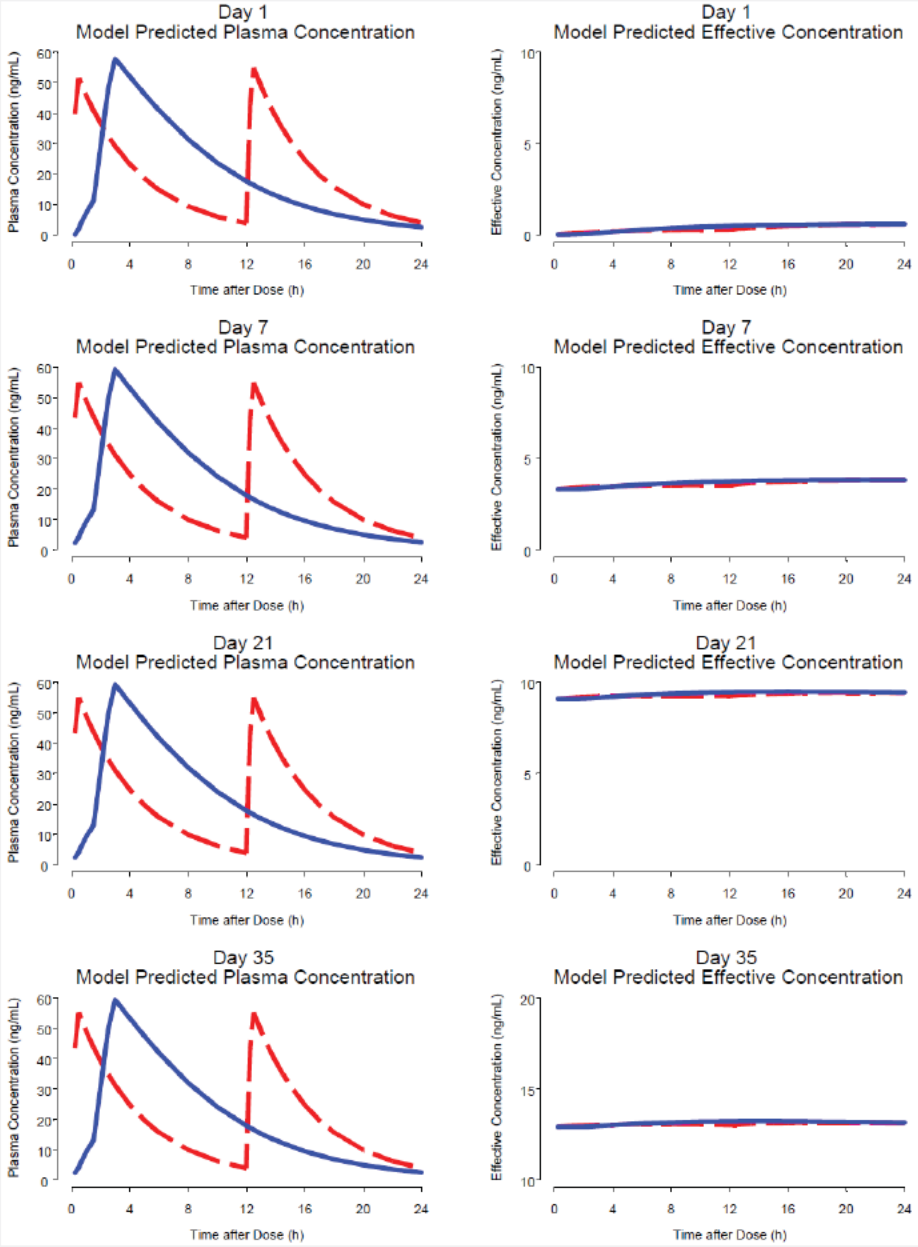
Transformed estimates are based on $exp(\cdot)$ except for the variance components of the random effects (η). Transformed estimates for the variance components are computed using a smoothed parametric bootstrap (simulating from a multivariate normal), and computing the CV and correlation (rho) from these simulations. Parameters with Transformed Units = Frac should be interpreted to indicate multiplicative factors modifying the reference parameter (see model above). For example, the Transformed Estimate for EMAX 1019 indicates that Study 1019 has an Emax effect of 0.866×EMAX = 0.866×0.454 = 0.393, and the EMAX = 0.454 indicates that the 54.6% reduction in DAS28 response relative to the placebo dose group is predicted for the typical individual for large doses at any given time point.

ED50 is estimated with respect BID dose amounts.

(Source: Table 4, appendix 2, summary clin pharm)

The DAS28 model described above confirms there is hysteresis or delay in pharmacodynamic (PD) onset (drug effect) relative to drug administration and drug accumulation (note that for tofacitinib steady state PK is achieved by the second day of

dosing). In the DAS28 model above, the effect of dose is infused over time, with an approximately 1 week half-life of equilibration (for lower doses), up to approximately 3 weeks for total daily dose of 10 mg. Therefore, one can conclude that the steady state PD effect of tofacitinib is achieved at a minimum of approximately 5 weeks after beginning administration. The PD delay of weeks relative to achieving PK steady state after 1 day for IR is substantial. Effective dose or effective concentration appears to be driving the PD effects.



The red dashed lines represent the IR 5 mg BID dose and the blue lines represent the MR 11 mg QD.

Figure 24. Model Predicted Plasma and Effective Concentration-Time Profiles by Day following IR 5 mg BID and MR 11 mg QD Administrations
(Source: Figure 2, Appendix 2, Summary of Clin pharm)

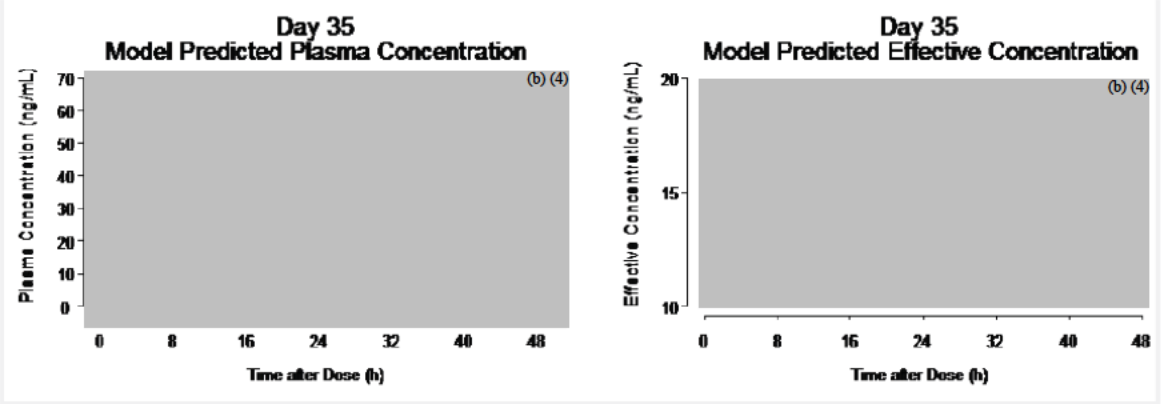
Reviewer's comments: *The kinetic-pharmacodynamic (KPD) model, built based on efficacy and PK data with BID regimens, did not describe the immediate effects of tofacitinib on plasma inflammatory mediators and the more sustained impact on chemotactic proteins. The model relied on the slow built-up and offset of clinical response (DAS28) relative to tofacitinib PK, and assumed that the daily or weekly variation in JAK 1/3 inhibition did not affect* (b) (4) *clinical response (Emax or EC50). With the data from study 1025, we agree that this is true for the QD and BID dosing regimen. The sponsor also assumed that the slow onset and offset of clinical response was driven by the effective dose at the action site. However, the slow onset and offset of clinical response may be a combination effect of disease characteristics and drug activity, as it was also observed in the placebo groups. Overall, while the model describes the DAS28 longitudinal data reasonably well, we need to use caution for interpretation of effective concentrations (Figure 24) and extrapolations for alternative dosing regimens other than QD or BID dosing interval, due to the many assumptions used in the model.*

Sponsor's Justification for dose recommendation in special populations

The KPD model was further employed to explore the model predicted effective concentrations of tofacitinib IR 5 mg QD (b) (4) Using an effect site link to account for delay between exposure and DAS28-3 (CRP) response as predicted by the model, the resultant effective concentration profile for the MR and IR formulations were compared. A dosing adjustment scenario was simulated by applying a 50% reduction in oral clearance compared to a typical RA patient profile (CL/F of 20.6 L/hour [PMAR-00178, NDA 203214]). This is representative of reduced clearance due to the patient-specific conditions (e.g. drug-drug interactions with potent CYP3A4 inhibitors) which necessitate a dose adjustment with tofacitinib.

The simulation results for a typical individual are displayed in Figure 25 that shows time course for model-predicted plasma and effective concentrations at steady state following repeated administration of either IR 5 mg QD (b) (4) (b) (4)

(b) (4)



The red dashed lines represent the IR 5 mg QD dose and the blue lines represent (b) (4).

Figure 25. Model Predicted Plasma (Left Panel) and Effective Concentrations (Right Panel) following IR 5 mg QD (b) (4)
(Source: Figure 1, IR response to NDA208246)

Reviewer's comments: *The kinetic-pharmacodynamic (KPD) model, built based on efficacy and PK data with BID regimens, did not describe the immediate effects of tofacitinib on plasma inflammatory mediators and the more sustained impact on chemotactic proteins. The model relied on the slow built-up and offset of clinical response (DAS28) relative to tofacitinib PK, and assumed that the daily or weekly variation in JAK 1/3 inhibition did not affect* (b) (4) *clinical response. While we agreed that the pharmacodynamic effect of tofacitinib appears to last longer than the PK half- life, we also noted that the pharmacodynamic effect preceded clinical response, and may be more sensitive to changes in dosing regimens. The slow onset and offset of clinical response may be the combination effect of disease characteristics and drug activity, and we should use caution to translate the slow onset of clinical response into* (b) (4) *when there is no safety or efficacy data to support the* (b) (4)

4.2 INDIVIDUAL STUDY REVIEW

1. Pivotal PK study

Trial # A3921212

Title: A Phase 1, Randomized, Open Label, 2-Period Crossover Study to Evaluate Single Dose and Steady State Pharmacokinetics and Bioavailability of the Modified Release Formulation of Tofacitinib Compared to the Immediate Release Formulation of Tofacitinib in Healthy Volunteers

- **Objectives**

To demonstrate the equivalence of the extent of exposure between a single dose of tofacitinib MR 11 mg relative to tofacitinib IR 10 mg administered as two 5 mg doses approximately 12 hours apart.

- **Study design and treatment schedule:**

A The study was a Phase 1, randomized, open-label, 2-period, 2-way crossover study to evaluate the PK, BA, and safety of the tofacitinib MR 11 mg proposed-commercial tablet formulation administered as a single dose on Day 1 followed by QD dosing on Days 3 through 7, relative to tofacitinib IR 10 mg administered as two 5 mg doses, approximately 12 hours apart, on Day 1 followed by tofacitinib IR 5 mg BID dosing (approximately 12 hours apart, Figure 26) from Days 3 through 7 in healthy volunteers.

Subjects were randomized to 1 of 2 treatment sequences as described Table 28.

Table 28. Treatment Sequence Schema

Sequence (Total N=24)	Period 1	Washout	Period 2
1 (n=12)	Treatment A (MR)[a]	At least 72 hours from the AM dose on Day 7	Treatment B (IR)[b]
2 (n=12)	Treatment B (IR)[b]	At least 72 hours from the AM dose on Day 7	Treatment A (MR)[a]

(Source: Table 1, Study report A3921212)

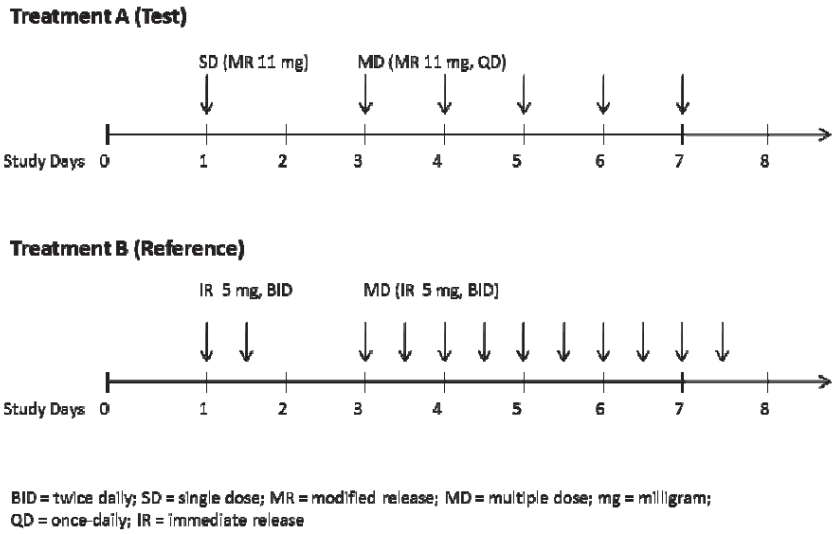


Figure 26: Treatment Dosing Schema

(Source: Figure 1, study report A3921212)

- **PK Sampling Schedule**

Single dose: Predose, 0.5, 1, 2, 3, 4, 6, 9, 12, 12.5, 13, 14, 15, 16, 18, 21, 24, 36, and 48 hours postdose.

Multiple dose (dosing on day 3-7): Day 3, day 5 and day 6: Predose before morning dose; Day 7: Predose, 0.5, 1, 2, 3, 4, 6, 9, 12, 12.5, 13, 14, 15, 16, 18, 21, and 24 hours postdose.

- **Results and Conclusions**

PK Results after Single Dose

Median plasma tofacitinib concentration-time profiles following single dose administration on Day 1 are presented in Figure 27 and PK parameters are summarized descriptively in Table 29.

Following administration of tofacitinib MR 11 mg (single oral dose) and tofacitinib IR 10 mg (2 tablets of 5 mg administered approximately 12 hours apart), peak concentrations after the morning dose (C_{max} for MR and $C_{max}1$ for IR) were similar. Peak concentrations were reached later for the MR treatment (median T_{max} = 4 hours) than for the IR treatment (median $T_{max}1$ = 0.5 hours) and terminal half-life was longer for the MR formulation (mean 5.9 hours) compared to the IR formulation (mean 3.2 hours). Total plasma tofacitinib exposure based on geometric mean AUC_{inf} was similar for both treatments (Table 29). Following the second tofacitinib IR 5 mg dose at 12 hours, peak (evening) concentrations for the IR treatment ($C_{max}2$) were approximately 30% lower than peak ($C_{max}1$) after the morning dose and were reached more slowly, with median $T_{max}2$ observed 2 hours post-evening dose (14 hours post-morning dose).

Results of the statistical analysis are summarized in Table 30. The 90% CIs for the

ratio (MR/IR) of adjusted geometric means for AUC_{inf} and C_{max} were within the 80% to 125% interval, demonstrating equivalence of tofacitinib total exposure for tofacitinib MR 11 mg and tofacitinib IR 5 mg X2.

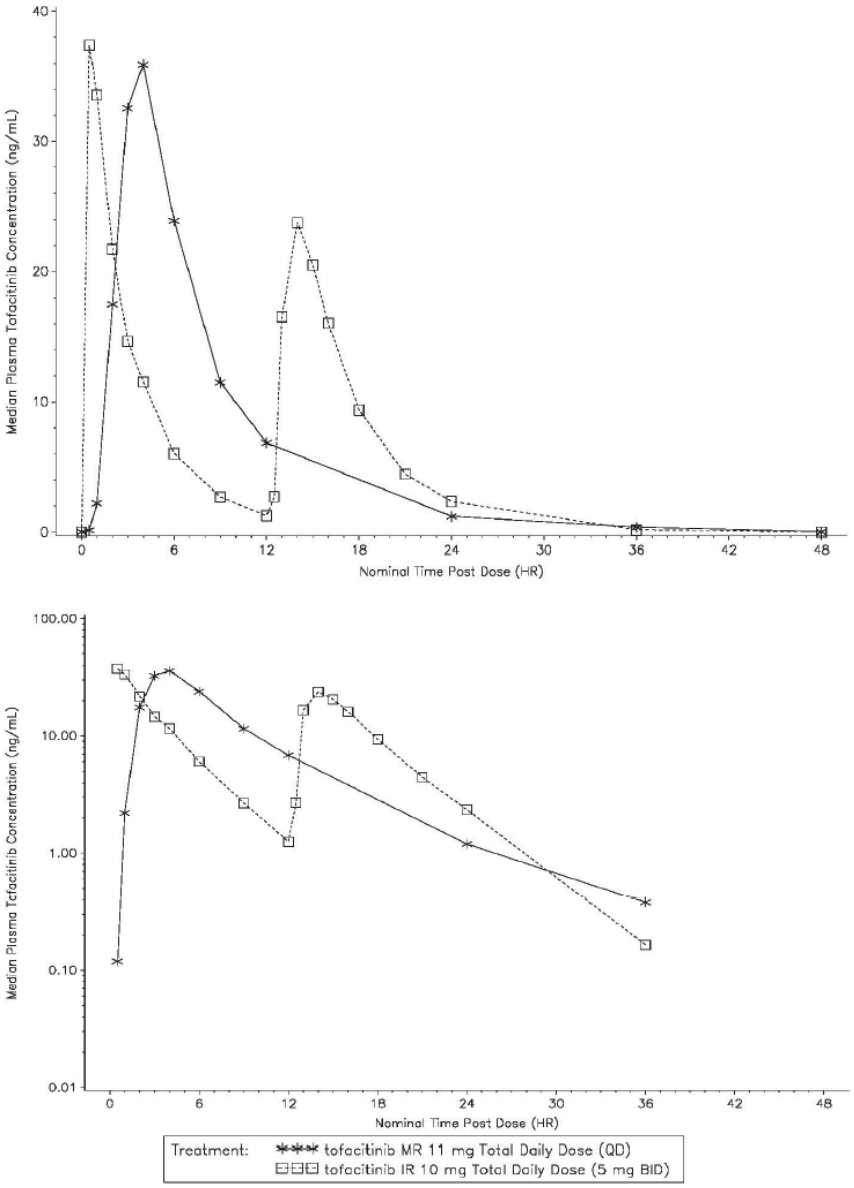


Figure 27: Median Plasma Tofacitinib Concentration-Time Profiles Following a Single Oral Dose of Tofacitinib MR 11 mg and Two Separate Oral Dose Administrations of Tofacitinib IR 5 mg (12 hours apart) on Day 1

(Source: Figure 2, study report A3921212)

Table 29. Descriptive Summary of Plasma Tofacitinib Pharmacokinetic Parameter Values for a Single Oral Dose of Tofacitinib MR 11 mg and Two Separate Oral Dose Administrations of Tofacitinib IR 5 mg (12 hours apart) on Day 1

	Parameter Summary Statistics[a] by Treatment			
	Tofacitinib MR 11 mg Total Daily Dose	Tofacitinib IR 10 mg Total Daily Dose (5 mg BID)		
Parameter (Unit)	All Data (0-48 hr)	All Data (0-48 hr)	Interval 1 Morning 0-12 hr[b]	Interval 2 Evening 12-24 hr[b]
N	23	24	24	24
AUC_{inf} (ng.hr/mL)	253.3 (24)	243.7 (20)	NA	NA
AUC_{last} (ng.hr/mL)	250.9 (24)	241.4 (20)	NA	NA
AUC_{24} (ng.hr/mL)	241.1 (22)	234.2 (19)	NA	NA
AUC_{τ} (ng.hr/mL)[c]	241.1 (22)	NA	115.8 (20)	118.4 (19)
$t_{½}$ (hr)	5.890±1.807	3.208±0.814	NA	NA
C_{max} (ng/mL)	36.10 (18)	40.15 (24)	39.22 (27)	27.96 (21)
T_{max} (hr)	4.00 (3.00-4.02)	0.500 (0.500-13.0)[d]	0.500 (0.500-1.00)	2.00 (0.5- 4.00)[e]

(Source: Table12, study A3921212 CSR)

Table 30. Statistical Summary of Treatment Comparisons for Plasma Tofacitinib Parameters Following a Single Oral Dose of Tofacitinib MR 11 mg and 2 Separate Oral Dose Administrations of Tofacitinib IR 5 mg (12 hours apart) on Day 1

	Adjusted Geometric Means			
Parameter (units)	Tofacitinib MR 11 mg (Test)	Tofacitinib IR 10 mg (5 mg BID) (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{inf} (ng.hr/mL)	253.2	243.7	103.92	98.81, 109.28
AUC_{last} (ng.hr/mL)	250.8	241.4	103.90	98.87, 109.19
C_{max}[b] (ng/mL)	35.98	39.22	91.75	83.27, 101.09

(Source: Table13, study A3921212 CSR)

PK Results after Multiple Dose

Median plasma tofacitinib concentration-time profiles following administration of tofacitinib MR 11 mg QD and tofacitinib IR 5 mg BID for 5 days are presented in Figure 28 and PK parameters are summarized descriptively in Table 31.

Following administration of tofacitinib MR 11 mg QD and tofacitinib IR 5 mg BID for 5 days, the overall results were consistent with those described above for Day 1 (single dose phase). Total daily plasma tofacitinib exposure based on AUC24 was similar for both treatments. Peak concentrations for Day 7 (C_{max} for MR and $C_{max}1$ for IR) were also similar with median T_{max} of 4 hours for MR and median $T_{max}1$ of 0.5 hours for IR, the same as on Day 1. Following the second tofacitinib IR 5 mg dose at 12 hours, peak (evening) concentrations for the IR treatment ($C_{max}2$) were approximately 20% lower than peak ($C_{max}1$) after the morning dose and were reached slightly later with median $T_{max}2$ observed 1 hour post-evening dose (13 hours post-morning dose).

Results of the statistical analysis are summarized in Table 32. The 90% CIs for the ratio (MR/IR) of adjusted geometric means for AUC_{24} and C_{max} values (C_{max} for MR and $C_{max}1$ for IR) were within the 80% to 125% interval, demonstrating equivalence

of tofacitinib total daily exposure for tofacitinib MR 11 mg QD and tofacitinib IR 5 mg BID.

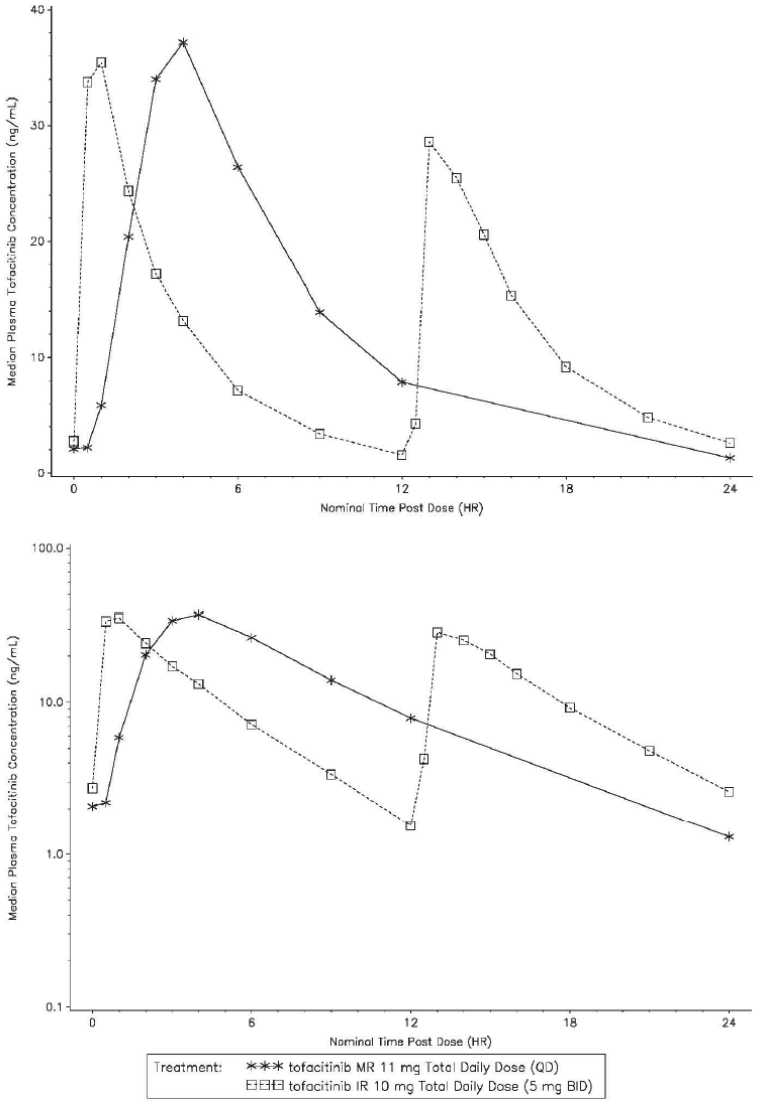


Figure 28: Median Plasma Tofacitinib Concentration-Time Profiles For Tofacitinib MR 11 mg Once Daily and Tofacitinib IR 5 mg BID on Day 7 (Day 5 of Multiple Dosing)

(Source: Figure 4, study report A3921212)

Table 31. Descriptive Summary of Plasma Tofacitinib Pharmacokinetic Parameter Values for Tofacitinib MR 11 mg QD and Tofacitinib IR 5 mg BID on Day 7 (Day 5 of Multiple Dosing)

	Parameter Summary Statistics[a] by Treatment			
	Tofacitinib MR 11 mg QD	Tofacitinib IR 5 mg BID		
Parameter (units)	All Data (0-24 hr)	All Data (0-24 hr)	Interval 1 Morning 0-12 hr[b]	Interval 2 Evening 12-24 hr[b]
N	23	24	24	24
AUC_{24} (ng.hr/mL)	269.0 (18)	263.4 (15)	NA	NA
AUC_{τ} (ng.hr/mL)[c]	269.0 (18)	NA	131.6 (17)	131.5 (15)
C_{av} (ng/mL)	11.20 (18)	10.97 (15)	10.96 (17)	10.95 (15)
C_{min} (ng/mL)[d]	1.067 (69)	1.407 (40)	1.478 (39)	1.407 (40)
C_{trough} (ng/mL)	1.840 (76)	2.475 (48)	NA	NA
C_{24} (ng/mL)	1.208 (72)	2.245 (41)	NA	NA
C_{max} (ng/mL)	38.23 (15)	42.69 (26)	40.89 (26)	33.40 (24)
T_{max} (hr)[e]	4.00 (3.00-4.00)	1.00 (0.500-14.0)[e]	0.500 (0.500-1.00)	1.0 (0.5-4.0)[f]
PTF	3.300 (16)	3.751 (22)	3.583 (23)	2.911 (20)
PTR	35.84 (63)	30.34 (42)	27.68 (43)	23.74 (40)
PTS	34.66 (66)	29.26 (43)	26.60 (45)	22.66 (42)

(Source: Table14, study A3921212 CSR)

Table 32. Statistical Summary of Treatment Comparisons for Plasma Tofacitinib Parameters for Tofacitinib MR 11 mg QD and Tofacitinib IR 5 mg BID on Day 7 (Day 5 of Multiple Dosing)

	Adjusted Geometric Means			
Parameter (units)	Tofacitinib MR 11 mg QD (Test)	Tofacitinib IR 5 mg BID (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
AUC_{24} (ng.hr/mL)	268.5	263.4	101.94	97.79, 106.27
C_{max}[b] (ng/mL)	38.19	40.89	93.41	84.14, 103.69
C_{trough} (ng/mL)	1.820	2.475	73.54	57.71, 93.70
C_{min}[b] (ng/mL)	1.044	1.478	70.64	59.01, 84.56

(Source: Table15, study A3921212 CSR)

- **Conclusions**
  - The extent of exposure for a single dose of tofacitinib MR 11 mg was equivalent to the two tofacitinib IR 5 mg doses approximately 12 hours apart, based on the 90% CI for the ratio (MR/IR) of adjusted geometric means for AUC_{inf} and C_{max} being wholly within equivalence limits (80% to 125%).

  - The steady-state extent of exposure for tofacitinib MR 11 mg QD was equivalent to tofacitinib IR 10 mg (5 mg BID), based on the 90% CI for the ratio (MR/IR) of adjusted geometric means for AUC_{24} and C_{max} being wholly within equivalence limits (80% to 125%).

  - Steady state for tofacitinib MR 11 mg formulation was achieved within 48 hours of QD dosing. There was minimal accumulation of systemic exposures upon repeated dosing.

  - The minimum plasma concentration (C_{min}) and predose plasma concentration (C_{trough}) at steady state are approximately 29% and 26% lower, respectively, for MR 11 mg QD compared to IR 5 mg BID.

Reviewer's comments: *Reviewer's independent analysis confirms that the 90% CI for the ratio (MR/IR) of adjusted geometric means for AUC and C_{max} being wholly within equivalence limits (80% to 125%) following single dose (day 1) and multiple dose (day 5).*

2. Other Relative Bioavailability (113, 131, 132, 163)

Trial # A3921113

Title: A Phase 1, Randomized, 3-Period, Open Label, Single Dose, Cross over Study to Evaluate the Pharmacokinetics and Safety of Two Controlled Release Formulations of CP-690,550

- **Objectives**

  To determine CP-690,550 pharmacokinetics (PK) following a 20-mg single oral dose given as 2 different controlled release (CR) formulations and a 10-mg single dose given as immediate release (IR) tablet.

- **Study design and treatment schedule:**

This was a Phase 1, randomized, 3-way crossover, single-dose, open-label study to compare the PK in healthy volunteers of 2 different CR CP-690,550 formulations to the IR tablet. Subjects were randomized to 1 of 6 treatment sequences as described in Table 33. A total of 12 healthy subjects (2 per sequence) were enrolled in the study.

Table 33. Treatment Sequences

Sequence	Period 1	Period 2	Period 3
1 (n=2)	A	B	C
2 (n=2)	A	C	B
3 (n=2)	B	C	A
4 (n=2)	B	A	C
5 (n=2)	C	A	B
6 (n=2)	C	B	A

(Source: Table S1, study A3921113 CSR)

- **PK Sampling Schedule**

Predose, 15min, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours postdose.

- **Results and Conclusions**

Median CP-690,550 concentration-time profiles for all treatments are presented in Figure 29. PK parameters are summarized descriptively in Table 34.

Based on the ratios of adjusted geometric mean dose normalized AUC_{inf} ($AUC_{inf(dn)}$) values, relative bioavailability was approximately 80.09% (90% CIs: 64.86%, 98.90%) and 55.39% (90% CIs: 44.59%, 68.81%) for the CR 6- hour and CR 12-hour formulations, respectively. The apparent terminal half-life was longer for CR

formulations than the IR. This is reflected in a mean half-life of 5.8 and 6.1 hours for the CR 6-hour and CR 12-hour formulations, respectively, as compared to 3.4 hours for the IR formulation.

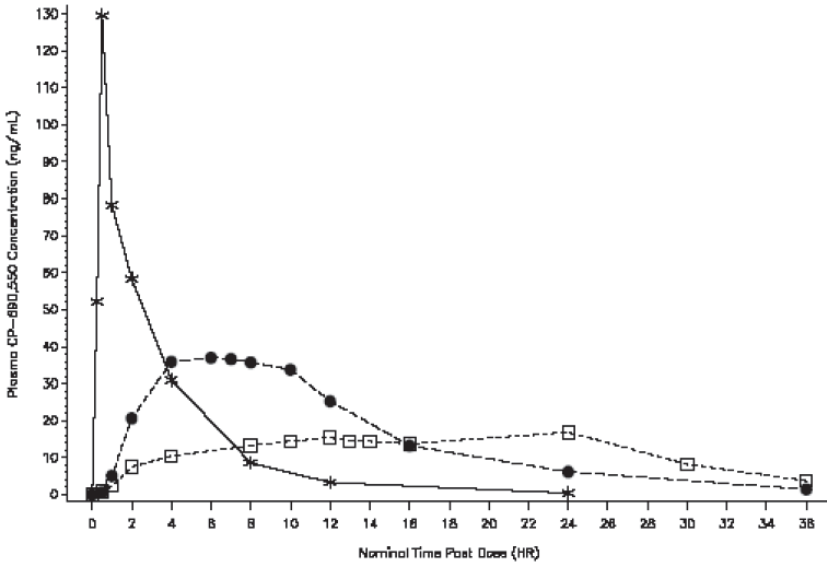


Figure 29: Median Plasma CP-690,550 Concentration-Time Profiles by Treatment Following Single Oral Doses

(Source: Figure S1, study A3921113 CSR)

Table 34. Statistical Summary of Treatment Comparisons

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI[a] for Ratio
	Test	Reference		
CR 6-hour Capsule (Test) vs IR Tablet (Reference)				
$AUC_{inf(dn)}$ (ng·hr/mL/mg)[b]	27.19	33.95	80.09	(64.86, 98.90)
$AUC_{last(dn)}$ (ng·hr/mL/mg)	26.56	33.77	78.65	(64.31, 96.19)
$C_{max(dn)}$ (ng/mL/mg)	2.094	12.15	17.24	(14.73, 20.16)
CR 12-hour Capsule (Test) vs IR Tablet (Reference)				
$AUC_{inf(dn)}$ (ng·hr/mL/mg) [b]	18.80	33.95	55.39	(44.59, 68.81)
$AUC_{last(dn)}$ (ng·hr/mL/mg)	18.38	33.77	54.43	(44.50, 66.56)
$C_{max(dn)}$ (ng/mL/mg)	0.9113	12.15	7.50	(6.41, 8.77)

(Source: Table S6, study A3921113 CSR)

- **Conclusions**

The rate and extent of absorption from the osmotic capsules decreased with increasing duration of drug release. The two CR capsule formulations were not developed further due to suboptimal bioavailability.

Trial # A3921131

Title: A Phase 1, Randomized, Open Label, Partial Crossover Study to Evaluate the Pharmacokinetics (PK) and Safety of Three Modified Release (MR) and One Immediate Release (IR) Formulations of Tofacitinib (CP-690,550) in Healthy Volunteers

- **Objectives**
  - To evaluate the PK of tofacitinib (CP-690,550) under fasting conditions following a 22-mg single oral dose of 3 different MR formulations: (1) MR-A; (2) MR-B1; (3) MR-B2; and (4) a 10-mg single oral dose of the current IR formulation.
  - To assess the effect of a high-fat meal on 2 different MR technologies, MR-A and MR-B1.
  - To estimate the relative bioavailability of the 3 different MR formulations (MR-A, MR-B1, MR-B2) relative to the IR formulation of tofacitinib (CP-690,550).

- **Study design and treatment schedule:**

This was a Phase 1, randomized, open label, 4-period, 6-sequence, partial cross-over, single-dose study to evaluate the PK of 3 MR formulations as compared to the IR formulation of tofacitinib under fasting conditions. The effect of food on the PK from MR-A and MR-B1 formulations was also assessed.
Subjects were randomized to 1 of the 6 treatment sequences as described in Table 35. A total of 30 healthy subjects (5 per sequence) were enrolled in the study.

Table 35. Study Sequence Schema

Sequence (Total N=30)	Period 1 (Fed)	Period 2(Fasted)	Period 3(Fasted)	Period 4(Fasted)
1 (N=5)	A	C	D	F
2 (N=5)	A	C	E	F
3 (N=5)	B	D	E	F
4 (N=5)	B	D	C	F
5 (N=5)	A	E	C	F
6 (N=5)	B	E	D	F

(Source: Table 1, study A3921131 CSR)

- **PK Sampling Schedule**

Predose, 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 36, 48 and 72 hours postdose.

- **Results and Conclusions**

Median plasma tofacitinib concentration-time profiles for all treatments are presented in Figure 30. Plasma tofacitinib PK parameters are summarized descriptively in Table 36.

All 3 MR formulations (MR-A, MR-B1, and MR-B2) resulted in later T_{max} compared to the IR formulation. For all 3 formulations, the estimated daily exposure of tofacitinib following once-daily oral dose of 22mg MR tablet is similar to estimated exposure of twice-daily administration of 10mg IR tablets. Based on the ratios of model adjusted geometric mean $AUC_{inf\ (adj)}$ values, relative total daily exposure were 100.35%, 106.00%, and 98.53% for MR-A, MR-B1, and MR-B2, respectively, and the 90% CIs were within (80%, 125%) for all 3 formulations.

Coadministration with a high-fat meal increased C_{max} for the MR-A formulation by 13% (ratio: 113.09%, 90% CI: 99.54%, 128.48%) with no change in AUC_{inf} (ratio: 100.22%, 90% CI: 94.86%, 105.90%). For the MR-B1 formulation, a high-fat meal

increased C_{max} by 53% (ratio: 153.33%, 90% CI: 134.97%, 174.20%) with no effect on AUC_{inf} (ratio: 104.50%, 90% CI: 98.91%, 110.42%) (Table 37).

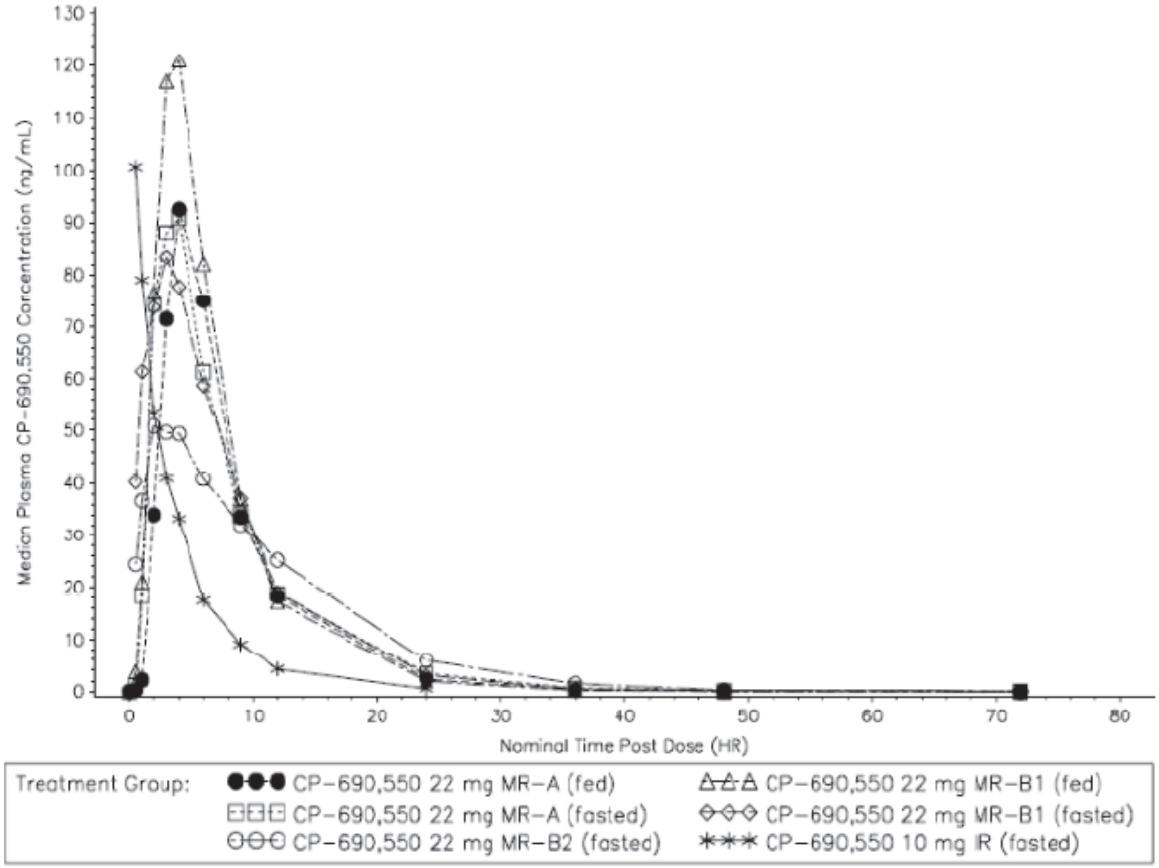


Figure 30: Median Plasma CP-690,550 Concentration-Time Profiles by Treatment Following Single Oral Doses

(Source: Figure 1, study A3921131 CSR)

Table 36. Total Daily Exposure Comparison: Dose adjusted AUC_{inf}, Dose adjusted AUC_{last}

Parameter (units)	Model Adjusted Geometric Means: 22-mg MR Fasted (Test)	Model Adjusted Geometric Means: 10-mg IR Fasted (Reference)	Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
MR-A vs IR				
AUC_{inf} adjusted (ng·hr/mL)	736.7	734.1	100.35	95.77, 105.16
AUC_{last} adjusted (ng·hr/mL)	735.1	727.5	101.05	96.47, 105.85
MR-B1 vs IR				
AUC_{inf} adjusted (ng·hr/mL)	778.2	734.1	106.00	101.16, 111.07
AUC_{last} adjusted (ng·hr/mL)	776.1	727.5	106.69	101.85, 111.76
MR-B2 vs IR				
AUC_{inf} adjusted (ng·hr/mL)	723.3	734.1	98.53	94.03, 103.24
AUC_{last} adjusted (ng·hr/mL)	719.6	727.5	98.93	94.44, 103.62

AUC_{last} adj and AUC_{inf} adj (fasted treatments only) = AUClast and AUC_{inf} adjusted for expected total daily exposure, assuming once-daily administration for MR formulations (adjusted values same as observed) and twice-daily administration for IR (adjusted values = 2 x observed).

(Source: Table 18, study A3921131 CSR)

Table 37. Statistical Summary of Treatment Comparisons for Food Effect

Parameter (units)	Model Adjusted Geometric Means: Fed (Test)	Model Adjusted Geometric Means: Fasted (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio (Test/Reference)
MR-A 22-mg fed vs fasted				
AUC_{inf} (ng.hr/mL)	739.1	737.5	100.22	94.86, 105.90
AUC_{last} (ng.hr/mL)	737.3	735.8	100.20	94.86, 105.84
C_{max} (ng/mL)	112.0	99.02	113.09	99.54, 128.48
MR-B1 22-mg fed vs fasted				
AUC_{inf} (ng.hr/mL)	815.0	779.9	104.50	98.91, 110.42
AUC_{last} (ng.hr/mL)	812.8	777.8	104.49	98.92, 110.37
C_{max} (ng/mL)	137.9	89.91	153.33	134.97, 174.20

(Source: Table 19, study A3921131 CSR)

- **Conclusions**

The relative bioavailability for all 3 MR formulations were 10% lower compared to for the IR formulation. A 10% increase in total daily dose for MR formulation was incorporated following analyses of these data to match the AUC between MR and IR formulations.

For all 3 formulations, the estimated daily exposure of tofacitinib following once-daily oral dose of 22mg MR tablet is similar to estimated exposure of twice-daily administration of 10mg IR tablets. Based on lack of food effect, MR-A was chosen for further development.

Trial # A3921132

Title: A Phase 1, Randomized, Open-Label, 2-Way, Crossover Study to Evaluate the Pharmacokinetics (PK), Safety, and Bioavailability of Tofacitinib Following Single Oral Dose of Modified-Release (MR) 11 mg Compared to MR 22 mg in Healthy Volunteers

- **Objectives**

  To evaluate the PK and estimate the bioavailability (BA) of tofacitinib following a single oral dose of MR 11 mg compared to a single oral dose of MR 22 mg in healthy volunteers in a fasted state.

- **Study design and treatment schedule:**

This was a Phase 1, randomized, open label, 2-period, 2-way cross-over study to evaluate the PK and safety of 2 doses (11 mg and 22 mg) of an MR formulation of tofacitinib in healthy volunteers under fasting conditions.

Subjects were randomized to 1 of the 2 treatment sequences as described in Table 38. A total of approximately 20 healthy subjects (10 per sequence) were enrolled in the study.

Table 38. Treatment Sequences

Sequence	Period 1	Washout	Period 2
1 (N = 10)	A	At least 72 hours	B
2 (N = 10)	B		A

Source: Section 16.1.1
Treatment A: Single oral dose of tofacitinib MR 11 mg tablet administered in the fasting state.
Treatment B: Single oral dose of tofacitinib MR 22 mg tablet administered in the fasting state.
(Source: Table 1, study A3921132 CSR)

- **PK Sampling Schedule**

Predose, 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 36, 48, and 72 hours.

- **Results and Conclusions**

PK parameters are summarized descriptively in Table 39.

Both MR tablet doses exhibited identical median T_{max} values of 3.0 hours and similar terminal t½ values of 6.3 hours and 7.3 hours for the MR 11 mg and MR 22 mg tablets, respectively. AUC_{inf} and C_{max} from MR 22 mg were approximately twice that of MR 11 mg, suggesting a linear and proportional increase in exposures with increase in dose. Tofacitinib exposures normalized for dose were essentially identical for both MR doses.

Table 39. Descriptive Summary of Plasma Tofacitinib Pharmacokinetic Parameter Values for MR 11 mg Tablets and MR 22 mg Tablets

	Parameter Summary Statistics[a] by Treatment	
Parameter (units)	**MR 11 mg (Test)**	**MR 22 mg (Reference)**
N	20	20
AUC_{inf} (ng.hr/mL)	315.6 (21)	645.8 (23)
AUC_{last} (ng.hr/mL)	313.7 (21)	641.1 (23)
C_{max} (ng/mL)	42.20 (32)	84.43 (22)
T_{max} (hr)	3.00 (2.00-4.00)	3.00 (2.00-4.00)
$t_{½}$ (hr)	6.250 ± 2.280	7.295 ± 3.375
$AUC_{inf\,(dn)}$ (ng.hr/mL/mg)	28.68 (21)	29.35 (23)
$AUC_{last\,(dn)}$ (ng.hr/mL/mg)	28.52 (21)	29.14 (23)
$C_{max\,(dn)}$ (ng/mL/mg)	3.837 (32)	3.838 (22)

(Source: Table 12, study A3921132 CSR)

- **Conclusions**

Tofacitinib MR has linear PK across doses 11 mg to 22 mg.

Trial # A3921163

Title: A Phase 1, Randomized, Open-Label, Single Dose, 2-Way Crossover Study in Healthy Volunteers to Evaluate the Pharmacokinetics, Bioavailability, and Safety of a Modified Release Formulation of Tofacitinib Compared to the Immediate Release Formulation of Tofacitinib

- **Objectives**

To determine the equivalence of extent of exposure of the tofacitinib MR 11 mg formulation compared to a 10 mg dose of the IR formulation in a fasted state.

- **Study design and treatment schedule:**

This was a Phase 1, open-label, randomized, 2-period, 2-treatment, 2-sequence crossover study.

Subjects were randomized to 1 of the 2 treatment sequences as described in Table 40. A total of 26 healthy subjects (13 per sequence) were enrolled in the study.

Table 40. Treatment Sequences

Sequence	Period 1	Washout	Period 2
1 (number of subjects = 13)	Treatment A	At least 72 hours	Treatment B
2 (number of subjects = 13)	Treatment B		Treatment A

Source: Protocol (Section 16.1.1)
Treatment A = single oral dose of tofacitinib MR 11 mg, administered as 1 × MR 11 mg tablet under a fasted condition.
Treatment B = single oral dose of tofacitinib IR 10 mg, administered as 2 × IR 5 mg tablets under a fasted condition.
(Source: Table 1, study A3921163 CSR)

- **PK Sampling Schedule**

Predose, 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours.

- **Results and Conclusions**

Median plasma tofacitinib concentration-time profiles are presented in Figure 31 and PK parameters are summarized descriptively in Table 41. As expected for a MR formulation, the peak concentrations occurred later for single dose of tofacitinib MR treatment (median T_{max}, 3.5 hours) than the IR treatment (median T_{max}, 0.5 hour). The arithmetic mean terminal t½ value was longer for MR treatment, with t½ of 5.7 hours, than the IR treatment, with t½ of 3.4 hours. The geometric mean C_{max}, adjusted for treatment, comparing peak exposure of MR 11 mg to that expected from a dose of IR 5 mg, was similar between MR (40.75 ng/mL) and IR (44.10 ng/mL) treatments. The geometric mean AUC_{inf} was also similar for both treatments (297.5 ng•hr/mL for MR and 286.3 ng•hr/mL for IR).

The ratios (MR Test/IR Reference) of adjusted geometric means (90% CIs) of tofacitinib AUC_{inf} and AUC_{last} were 103.91% (100.49%, 107.45%) and 103.55% (100.16%, 107.07%), respectively, with the 90% CIs wholly contained within the 80% to 125% interval, demonstrating equivalence of tofacitinib total exposure for MR 11 mg relative to the IR 10 mg dose (Table 42).

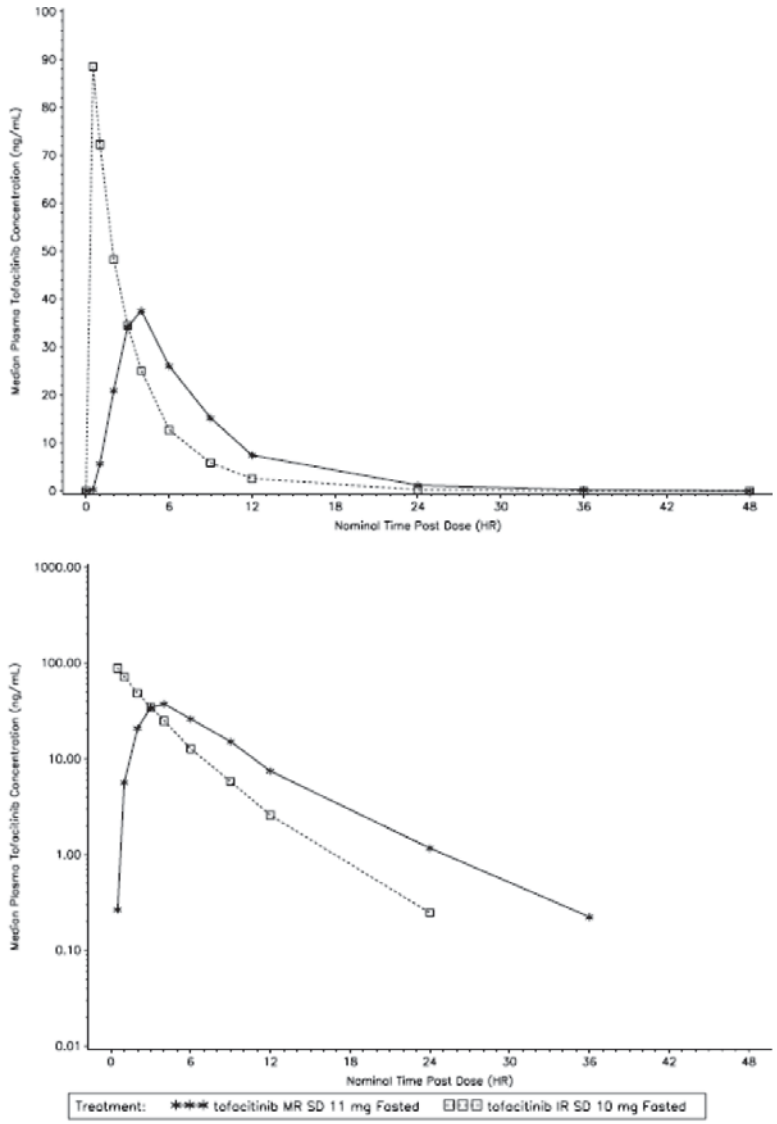


Figure 31: Median Plasma Tofacitinib Concentration-Time Profiles Following Single Oral Doses of MR 11 mg and IR 10 mg Formulations

(Source: Figure 1, study report A3921163)

Table 41. Descriptive Summary of Plasma Tofacitinib Pharmacokinetic Parameter Values for MR and IR Formulations

	Parameter Summary Statistics[a] by Treatment	
Parameter (Unit)	**Tofacitinib MR 11 mg (Test)**	**Tofacitinib IR 10 mg (Reference)**
N	26	26
C_{max} (ng/mL)	40.75 (29)	88.17 (29)
T_{max} (hr)	3.54 (3.00-6.00)	0.500 (0.500-2.00)
$C_{max(adj)}$ (ng/mL)	40.75 (29)	44.10 (29)
AUC_{last} (ng•hr/mL)	295.1 (23)	285.0 (21)
AUC_{inf} (ng•hr/mL)	297.5 (23)	286.3 (20)
$t_{½}$ (hr)	5.705 ± 2.311	3.413 ± 0.630

(Source: Table12, study A3921163 CSR)

Table 42. Statistical Summary of Treatment Comparisons for Plasma Tofacitinib Parameters Following Single Oral Doses of MR 11 mg and IR 10 mg Formulations

Parameter (Unit)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
	MR 11 mg (Test)	IR 10 mg (Reference)		
AUC_{inf} (ng•hr/mL)	297.5	286.3	103.91	100.49, 107.45
AUC_{last} (ng•hr/mL)	295.1	285.0	103.55	100.16, 107.07
$C_{max(adj)}$ (ng/mL)	40.75	44.10	92.40	84.99, 100.45

(Source: Table13, study A3921163 CSR)

- **Conclusions**

  Single dose of tofacitinib MR 11 mg formulation has equivalent exposure to tofacitinib IR 10 mg dose under the fasted state, as the 90% CI for the ratio (MR/IR) of the adjusted geometric means for AUC_{inf} and C_{max} was wholly contained within the 80% to 125% interval.

3. Food Effect with commercial formulation

Trial # A3921180

Title: A Phase 1, Randomized, Open Label, Single Dose, 2-Period Crossover Study to Evaluate the Effect of Food on the Pharmacokinetics of Tofacitinib Modified Release (MR) 11 mg Tablets in Healthy Western and Japanese Volunteers

- **Objective**

  To evaluate the effect of food on the pharmacokinetics (PK) of a single dose of the tofacitinib modified release (MR) 11 mg proposed-commercial tablet formulation.

- **Study design –**This was a Phase 1, randomized, open label, single dose, 2-treatment, 2-period, 2-sequence crossover study to evaluate the effect of food on the PK of tofacitinib MR 11 mg proposed-commercial tablet formulation in healthy Western and Japanese subjects. Subjects were randomized to 1 of the 2 treatment sequences as described in Table 43. Each treatment sequence consisted of 2 periods.

Table 43. Treatment Sequence

Sequence (Total N=24)	Period 1	Washout	Period 2
1 (n=12)	A (Fed)	At least 72 hours	B (Fasted)
2 (n=12)	B (Fasted)	At least 72 hours	A (Fed)

Treatment A = Single oral dose of tofacitinib MR administered as a 1 × 11 mg tablet under fed conditions.
Treatment B = Single oral dose of tofacitinib MR administered as a 1 × 11 mg tablet under fasted conditions.
(Source: Table 1, Study report A3921180)

- **PK Sampling Schedule**

PK blood samples were collected at predose (0), 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours post dose in Periods 1 and 2.

- **Results and Conclusions**

PK results

Median plasma tofacitinib concentration-time profiles for Day 1 are presented in Figure

32.

In the presence of food, absorption was slightly delayed. Following administration of a single tofacitinib MR 11 mg dose under fed and fasted conditions, total plasma tofacitinib exposure based on geometric mean AUC_{inf} was similar for both treatments (Table 44). Peak concentrations for the fed treatment were higher than those for the fasted treatment and were reached 1 hour later (median T_{max} was 4 hours for the fed treatment versus 3 hours for the fasted treatment). Mean t½ was 4.4 hours for the fed treatment and 5.5 hours for the fasted treatment.

Table 44. Statistical Summary of Treatment Comparisons for Plasma Tofacitinib Parameters Following a Single Oral Dose of Tofacitinib MR 11 mg under Fed and Fasted Conditions

	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
Parameter (Units)	Fed (Test)	Fasted (Reference)		
AUC_{inf} (ng•hr/mL)	268.6	265.6	101.11	96.94, 105.46
AUC_{last} (ng•hr/mL)	266.6	263.5	101.19	96.92, 105.65
C_{max} (ng/mL)	47.09	37.02	127.21	116.57, 138.83

(Source: Table 13, study A3921180 CSR)

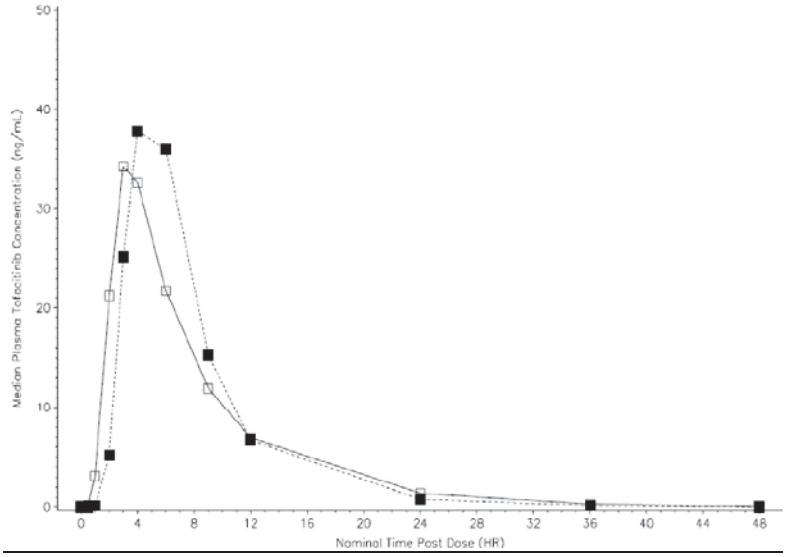


Figure 32. Median Plasma Tofacitinib Concentration-Time Profiles Following a Single Oral Dose of Tofacitinib MR 11 mg under Fasted and Fed Conditions
(Source: Figure 1, study A3921180 CSR)

- **Conclusions**

The Co-administration of the proposed-commercial tablet formulation of tofacitinib MR 11 mg with a high fat meal had no impact on the overall exposure of tofacitinib.

4.3 FILING MEMO

Application Information			
NDA/BLA Number	208246	**SDN**	
Applicant	Pfizer	**Submission Date**	4/24/2015
Generic Name	Tofacitinib MR	**Brand Name**	Xeljanz XR
Drug Class	inhibitor of Janus kinases (JAKs)		
Indication	Moderate to severe active RA		
Dosage Regimen	11 mg qd		
Dosage Form	MR tablets (11mg)	**Route of Administration**	Oral
OCP Division	II	**OND Division**	Pulmonary, Allergy, and Rheumatology Products
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Jianmeng Chen	Ping Ji	
Pharmacometrics	Jianmeng Chen	Yaning Wang	
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	6/23/2015	**74-Day Letter Date**	7/7/2015
Review Due Date	1/20/2016	**PDUFA Goal Date**	2/24/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

1. We acknowledge that the proposed tofacitinib MR 11 mg QD appeared to exhibit comparable Cmax and AUC relative to tofacitinib IR 5 mg BID. However, the Cmin of tofacitinib MR 11 mg QD was about 30% lower than that observed with tofacitinib IR 5 mg BID. We also note that the overall tofacitinib concentration time profile of tofacitinib MR 11 mg QD was not similar to that of tofacinitib IR 5 mg BID. You have to provide appropriate justification that these differences do not inadvertently impact the safety and efficacy profiles of the proposed formulation and the once daily dosing regimen of tofacitinib MR 11 mg QD in

comparison to the approved tofacitinib IR 5 mg BID. The adequacy of this justification will be reviewed along with the application.

2. You have proposed [redacted] (b) (4) (b) (4) You have to provide appropriate justification that this difference does not impact the safety and efficacy of tofacitinib. The adequacy of this justification will be a review issue.

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

OSI inspection will be requested for study A3921212 (clinical site) and A3929023 (analytical lab).

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☑ Relative Bioavailability	4	A3921163, A3921113, A3921131 and A3921132
☑ Bioequivalence	1	Pivotal PK bridging study: A3921212
☑ Food Effect	1	A3921180

☑ Other		2	A3921195, IVIVC, to be reviewed by biopharm; Analytical Method A3929023 will be reviewed
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☑ Population Pharmacokinetics		15	Sponsor provided additional reports/datasets to answer IR
☑ Exposure-Efficacy		4	Appendix 1-4
☐ Exposure-Safety			

Total Number of Studies and reports	**In Vitro**		**In Vivo**	27
Total Number of Studies/reports to				26

be Reviewed				

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIANMENG CHEN
01/20/2016

YANING WANG
01/20/2016

PING JI
01/21/2016

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208246	**SDN**	
Applicant	Pfizer	**Submission Date**	4/24/2015
Generic Name	Tofacitinib MR	**Brand Name**	Xeljanz XR
Drug Class	inhibitor of Janus kinases (JAKs)		
Indication	Moderate to severe active RA		
Dosage Regimen	11 mg qd		
Dosage Form	MR tablets (11mg)	**Route of Administration**	Oral
OCP Division	II	**OND Division**	Pulmonary, Allergy, and Rheumatology Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Jianmeng Chen	Ping Ji
Pharmacometrics	Jianmeng Chen	Yaning Wang
Genomics		

Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	6/23/2015	**74-Day Letter Date**	7/7/2015
Review Due Date	1/20/2016	**PDUFA Goal Date**	2/24/2016

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☑ Yes

☐ No

1. We acknowledge that the proposed tofacitinib MR 11 mg QD appeared to exhibit comparable Cmax and AUC relative to tofacitinib IR 5 mg BID. However, the Cmin of tofacitinib MR 11 mg QD was about 30% lower than that observed with tofacitinib IR 5 mg BID. We also note that the overall tofacitinib concentration time profile of tofacitinib MR 11 mg QD was not similar to that of tofacinitib IR 5 mg BID. You have to provide appropriate justification that these differences do not inadvertently impact the safety and efficacy profiles of the proposed formulation and the once daily dosing regimen of tofacitinib MR 11 mg QD in comparison to the approved tofacitinib IR 5 mg BID. The adequacy of this justification will be reviewed along with the application.

2. You have proposed (b) (4) (b) (4) You have to provide appropriate justification that this difference does not impact the safety and efficacy of tofacitinib. The adequacy of this justification

will be a review issue.

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

OSI inspection will be requested for study A3921212 (clinical site) and A3929023 (analytical lab).

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☐ Transporter Characterization		
☐ Distribution		
☐ Drug-Drug Interaction		
In Vivo Studies		
Biopharmaceutics		
☐ Absolute Bioavailability		
☑ Relative Bioavailability	4	A3921163, A3921113, A3921131 and A3921132
☑ Bioequivalence	1	Pivotal PK bridging study: A3921212
☑ Food Effect	1	A3921180
☑ Other	2	A3921195, IVIVC, to be reviewed by biopharm; Analytical Method A3929023 will be reviewed
Human Pharmacokinetics		
Healthy Subjects ☐ Single Dose		
Healthy Subjects ☐ Multiple Dose		
Patients ☐ Single Dose		
Patients ☐ Multiple Dose		
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		

☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☐ QT		
Pharmacometrics		
☑ Population Pharmacokinetics	15	Sponsor provided additional reports/datasets to answer IR
☑ Exposure-Efficacy	4	Appendix 1-4
☐ Exposure-Safety		

Total Number of Studies and reports	**In Vitro**		**In Vivo**	27
Total Number of Studies/reports to be Reviewed				26

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	The reference product Xeljanz is by the same sponsor, and this is a 505(b)(1) submission
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	Method A3929023 was used to support pivotal PK study A3921212
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	We have issued an IR for items recommended in the pre-NDA meeting. Sponsor has answered part of the IR, and will address the rest of IR by July 31st.

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo

Submission in brief:

Indication and mechanism of action

This application seeks approval for the tofacitinib modified release (MR) 11 mg once daily (QD) tablet formulation for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate. The proposed MR Formulation provides a QD dosing alternative to Xeljanz®, the currently approved tofacitinib immediate release (IR) tablet formulation (NDA203214, approved Nov 6, 2012) administered 5 mg twice daily (BID).

There have been several interactions between Agency and Sponsor to discuss the overall development program for the proposed product as listed in Table 1.

Table 1. Summary of Regulatory history relevant to clinical pharmacology!

PNDA (Dec 2014)	Agreed on general clinical pharm studies adequate to support NDA filing. Recommend PK/PD analysis to include both QD and BID dosing regimen. Recommend PK/PD analysis to explore additional endpoints, such as ACR20, 50, 70.
Pre-IND (Mar 2013)	"Based on the PK profile and E-R, a clinical study may not add meaningful information and may not be necessary."

Summary of information submitted

The MR clinical program was comprised of seven Phase 1 biopharmaceutic studies in healthy volunteers. These studies evaluated the following:

1. Feasibility of administering tofacitinib, a highly soluble drug, as an MR formulation (Study A3921113);
2. PK of pilot tofacitinib MR formulations (Studies A3921131 and A3921132);
3. Single dose PK and relative bioavailability (BA) of tofacitinib MR 11 mg tablets from an initial commercial-level scale manufacture, compared to IR 2x5 mg tablets (Study A3921163);
4. Effect of a high fat meal on the PK and BA of proposed-commercial tablet formulation of tofacitinib MR 11 mg (Study A3921180);
5. Single and multiple dose PK and relative BA of the proposed-commercial tablet formulation of tofacitinib MR 11 mg QD relative to IR 5 mg BID (Study A3921212);
6. Correlation of in-vitro dissolution with in-vivo plasma drug concentrations of MR tablet formulations with varying release rates (Study A3921195).

The clinical pharmacology review will focus on the six studies listed in item 1-5 above. The study A3921195 and the in vitro alcohol dumping study will be assessed in the biopharm review.

Effect of intrinsic/extrinsic factors

As per sponsor's proposal, (b) (4)

(b) (4)

This will be further evaluated in the clinical pharmacology review.

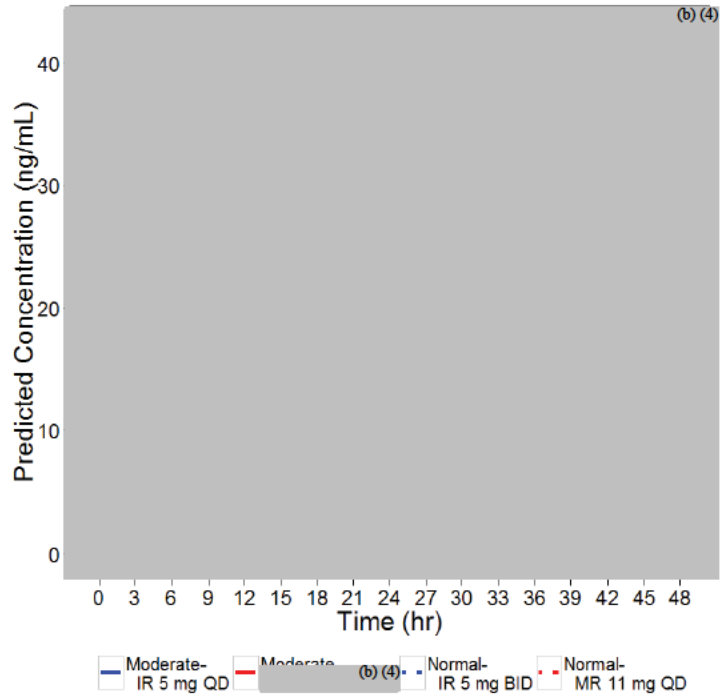


Figure 1. Simulated Tofacitinib Plasma Concentration-Time Profiles in Subjects with Normal Hepatic Function and Moderate Hepatic Impairment BID: Dosing recommendation for MR is based on simulation

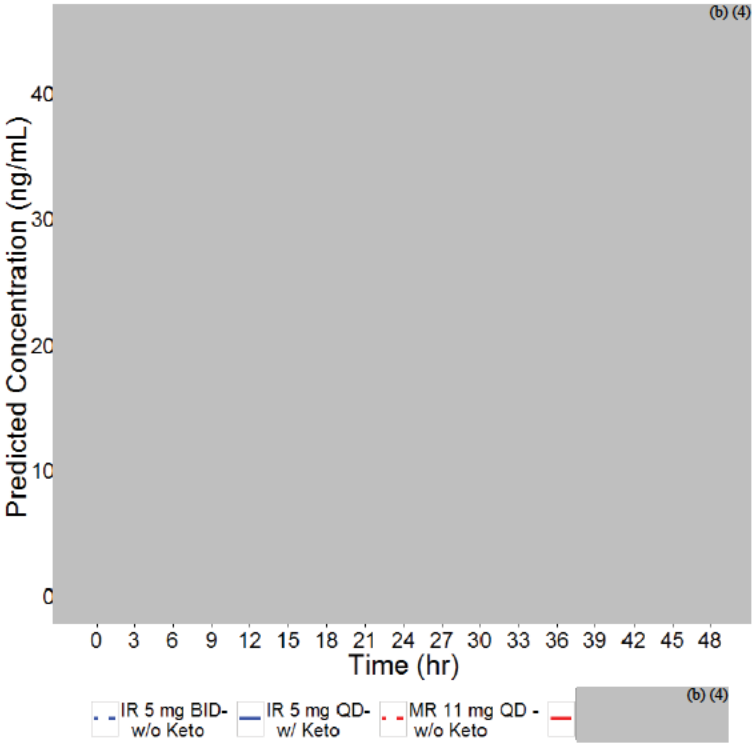


Figure 2: Simulated Tofacitinib Plasma Concentration-Time Profiles for Various Regimens with or without Ketoconazole: Dosing recommendation for XR is based on simulation

Pediatrics development plan

As agreed in the approved initial PSP (dated April 20, 2015), Pfizer will pursue the development of an age-appropriate tofacitinib MR formulation for QD dosing in pediatric patients requiring doses lower than 11 mg and/or pediatric patients who are unwilling/unable to swallow the current MR 11 mg tablet. Additionally, Pfizer

is requesting a waiver of pediatric studies for JIA in patients less than 2 years of age and proposes to defer any PREA-required studies and timelines until completion of Studies A3921103 and A3921104 (Pediatric studies for tofacitinib IR).

Summary of Tofacitinib_MR PK

Across the pilot and proposed commercial MR 11 mg (extrudable core system [ECS] osmotic) tablet formulations (Studies A3921131, A3921132, A3921163, A3921180, A3921195, and A3921212), the geometric mean Cmax and AUCinf ranged from 36.10- 42.20 ng/mL and 253-314 ng.hr/mL, respectively under fasting conditions; the median Tmax and mean t½ values ranged from 3.00-4.00 hours and 5.45-6.25 hours, respectively. In the single and multiple-dose PK study (A3921212), single and multiple-dose PK profiles of tofacitinib MR 11 mg formulation were nearly superimposable. Multiple dose to single dose accumulation ratios were approximately 1.06 and 1.12 for Cmax and AUC, respectively for the MR formulation, indicating negligible accumulation following repeat dosing of the tofacitinib MR formulation, which is similar to that observed for IR formulation. Trough (pre-dose) concentration monitoring indicates that steady state concentrations are achieved within 48 hours of repeat dosing of MR 11 mg QD.

Evaluation of relative BA for the MR 11 mg formulation compared to the IR 5 mg formulation has demonstrated equivalence of AUC and Cmax in pivotal PK study A3921212 (Table 2), as well as other studies (Section 2.7.1.3.1 Summary of Biopharmaceutics). At steady state, Cmin for MR 11 mg QD is approximately 29% lower and Ctrough is approximately 26% lower compared to IR 5 mg BID (Table 2).

Table 2. Summary of PK of Tofacitinib MR 11mg QD compared to Tofacitinib IR 5mg BID (study A3921212)

Parameter (Unit)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a] (%)	90% CI for Ratio
	MR 11 mg QD (Test)	IR 5 mg BID (Reference)		
Day 1 (Single Dose Phase)				
AUC_{inf} (ng•hr/mL)	253.2	243.7	103.92	98.81, 109.28
$C_{max(}$ (ng/mL)	35.98	39.22	91.75	83.27, 101.09
Day 5 (Multiple Dose Phase)				
AUC_{24} (ng•hr/mL)	268.5	263.4	101.94	97.79, 106.27
C_{max} (ng/mL)	38.19	40.89	93.41	84.14, 103.69
C_{min} (ng/mL)	1.044	1.478	70.64	59.01, 84.56
C_{trough} (ng/mL)	1.820	2.475	73.54	57.71, 93.70

a. The ratios (and 90% CIs) are expressed as percentages.

AUC_{inf} = Area under the plasma concentration-time profile from time zero extrapolated to infinite time; AUC_{24} = Area under the plasma concentration-time profile from time zero to 24 hours; C_{max} = maximum plasma concentration; C_{min} = Minimum plasma concentration; C_{trough} = Predose plasma concentration; CI = Confidence Interval; IR= Immediate Release; MR = Modified Release.

Summary of Exposure Response Analysis

Sponsor conducted exposure response analysis using data on different doses and dosing regimens (QD and BID) of the IR formulation from clinical and nonclinical studies previously submitted in NDA 203214. Sponsor reported findings from these analyses in four pop PK/PD reports (Appendix 1, 2, 3, 4). Based on the E-R relationships from the IR development program, sponsor tried to show that the slightly lower (29%) Cmin is not clinically important to the efficacy of tofacitinib; and to support the bridging of efficacy from IR 5 mg BID to MR 11 mg QD.

OSI inspection

OSI inspection will be requested for study A3921212 (clinical site) and A3929023 (analytical lab).

Mid-Cycle Deliverables

- Any approvability issues for this application
- Complete reviews of
    - PK equivalence
    - Exposure-Response Evaluation
    - Special population/DDI

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIANMENG CHEN
06/23/2015

PING JI
06/23/2015