CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	203214
Submission Date	10/21/2011
Brand Name	TBD
Generic Name	Tofacitinib
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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)	Tablet ; 5 mg and 10 mg
Indication	Rheumatoid Arthritis
Dosage Regimen	5 mg BID; some patients may benefit from an increase to 10 mg BID based on clinical response

1. Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology finds NDA 203214 acceptable

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Pfizer, Inc. has submitted NDA 203214 seeking marketing approval for tofacitinib. Tofacitinib is an orally administered Janus kinase (JAK) inhibitor with preferential activity against JAK1 and/or JAK3 over JAK2. If approved, it will be the first JAK inhibitor for treatment of rheumatoid arthritis.

Sponsor supported this NDA submission with 21 phase 1 studies, 5 phase 2 studies, 5 phase 3 studies (to support efficacy and safety), and 12 population based modeling analyses.

Pre-Clinical Support for Dose Selection

Data from mouse collagen-induced arthritis (CIA) model demonstrated that effective modulation of the inflammatory response through JAK1/3 inhibition may not require continuous coverage of tofacitinib (i.e., plasma tofacitinib concentrations in excess of IC_{50}). ED_{50} in animal models for BID vs. QD dosing regimen were 6-12.8 mg/kg and 33.5-40.5 mg/kg, respectively, and BID was anticipated to inhibit JAK1/3 signaling for longer duration than QD. Based on results from preclinical studies, sponsor designed the clinical program to optimize the BID dosing regimen.

Dose-Response

- A trend of increase in ACR20, ACR70, ACR90 and DAS28-3 response at week 12 was observed with increase in dose from 1 to 15 mg for treatment with tofacitinib monotherapy. When tofacitinib (from 3 mg BID to 15 mg BID and 20 mg QD) was administered in background of methotrexate, dose related changes in ACR 20, ACR50, ACR70 and DAS 28 were not observed.
- A trend of decrease in neutrophil counts and increase in LDLC, HDLC, total cholesterol and serum creatinine was observed with increase in dose for tofacitinib monotherapy. A similar dose-response relationship for lipid endpoints was also observed when tofacitinib was administered in background of methotrexate
- A trend of increase in hemoglobin was seen for lower doses up to 5 mg following which a decline was observed (i.e., an inverted U-shape relationship) with tofacitinib monotherapy. A similar dose-response relationship for hemoglobin was also observed when tofacitinib was administered in background of methotrexate

- Selection of dose was based on probability of achieving the target effect with respect to both efficacy (defined as placebo-adjusted response rate of at least 20% for ACR20, 20% for ACR50, and 15% for ACR70 at week 12) and safety (no more than 5% placebo-adjusted incidences of anemia through 24 weeks). 5 and 10 mg bid doses had approximately 50% probability of achieving the target effect
- ACR20, ACR50 and ACR90 responses observed in Phase 3 clinical trials were in similar range as observed in Phase 2 studies
- Trends for safety endpoints between 5 and 10 mg dose in Phase 3 trials were similar to that observed in Phase 2 studies
- Changes in CD3+, CD4+ and CD8+ cell counts were not dose dependent following tofacitinib treatment up to 24 weeks
- There was a trend of increase in Natural Killer cell (CD16+/56+ cell) counts with increase in dose
- There was a trend of decline in B cell (CD19+ cell) counts with increase in dose
- A decline was observed in IgG, IgM, and IgA levels following treatment with tofacitinib for 24 weeks compared to placebo; however, these changes were small and not dose-dependent

Pharmacokinetics

Rheumatoid Arthritis vs. Healthy

- Population PK analysis showed 43% lower apparent clearance (CL/F) in a typical RA patient relative to a healthy adult

Absorption

- The absolute bioavailability of tofacitinb at 10 mg dose was 74%
- Systemic exposure ($AUC_{0-\infty}$) and peak plasma concentration (C_{max}) increased in proportion to the dose in the dose range of 1 to 100 mg.
- T_{max} was reached by approximately 0.5-1 hours following oral administration
- Coadministration with food had no significant effect on the extent of absorption ($AUC_{0-\infty}$) but rate of absorption (C_{max}) was reduced by 32%.
- Upon multiple dosing, steady-state was reached by 24-48 hours with negligible accumulation
- Tofacitinib is a substrate of P-gp transporter

Distribution

- Tofacitinib has a total plasma protein binding of approximately 39%. Tofacitinib binds moderately to albumin and does not bind to alpha-1 acid glycoprotein.
- Steady-state volume of distribution (V_{dss}) for tofacitinib following iv infusion administration was 87 L, suggesting distribution into tissues.

Metabolism and Transporters

- Tofacitinib was extensively metabolized, primarily by CYP3A4 enzyme with minor contribution from CYP2C19
- All metabolites have less than <8% of total drug exposure and their potency was reported to be ≤10% of the potency of tofacitinib for JAK1/3 inhibition.

- Based on in vitro studies, tofacitinib is not a substrate of BCRP transporter.
- Based on in vitro studies, at therapeutic concentrations, tofacitinib has low potential for induction or inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 metabolic enzymes and low potential of inhibition for P-gp, OCT2, OATP1B1, OATP1B3

Elimination

- Of the 94% drug recovered following oral administration in a mass balance study, approximately 29% and 51% was recovered in urine as parent drug and metabolites, respectively. In feces, proportion of parent and metabolites recovered was approximately 1% and 13%.
- The terminal elimination half-life of tofacitinb was approximately 3 hours after single- or multiple-dose

Population Pharmacokinetic Analysis

- **Age**

Elderly patients age 70 years or 80 years were estimated to have less than 10% difference in AUC and C_{max} relative to the mean age of 55 years, after accounting for differences in renal function (i.e., creatinine clearance)

- **Weight**

Patients with extreme body weight 40 kg and 140 kg were estimated to have less than 5% difference in AUC relative to the mean weight of 70 kg, after accounting for differences in renal function (i.e., creatinine clearance)

- **Gender**

Women were estimated to have less than 7% difference in AUC and C_{max} compared to men, after accounting for differences in renal function (i.e., creatinine clearance)

- **Race**

Based on available data are no major differences were seen in tofacitinib AUC and C_{max} between White, Black and Asian patients, after accounting for differences in renal function (i.e., creatinine clearance)

Special Population

Renal Impairment

- Mean percentage change in AUC (90%CI), for subjects with mild, moderate, and severe renal impairment compared to normal renal function were respectively: 41% (-5%, 109%), 71% (14%, 157%), and 156% (69%, 287%). Mean percentage changes in Cmax (90% CI) for these cases were respectively: 1% (-31%, 49%), 2% (-31%, 52%), and 21% (-19%, 81%). At this point in time, additional safety analysis is ongoing and a final decision on the dosing regimen to be approved is pending. If both 5 and 10 mg BID doses are approved, tofacitinib dose should not exceed 5 mg BID in subjects with moderate and severe renal impairment. However, if only 5 mg BID is approved, a reduced tofacitinib dose of 5 mg QD is recommended in these subjects.

- A 14 days study was conducted to assess the impact of tofacitinib on renal function by measuring the glomerular filtration rate (iohexol serum clearance), effective renal plasma flow (by p-amino hippuric acid (PAH) clearance), and measured creatinine clearance (CLCr, based on 24-hour urine collection) on day 1 and day 15. No significant change in iohexol serum clearance, PAH clearance, and CLCr were observed with mean change of less than 10% for comparison of Day 15 vs. Day 1. Renal function is not affected at least following 14 days of treatment.

- ***Hepatic Impairment***
- Mean percentage change in AUC (90%CI) for subjects with mild and moderate hepatic impairment vs. normal hepatic function were respectively: 3% (-22%, 36%) and 65% (25%, 117%). Mean percentage change in C_{max} (90% CI) for these cases were respectively: -1% (-25%, 32%) and 49% (12%, 97%). If both 5 and 10 mg BID doses are approved, tofacitinib dose should not exceed 5 mg BID in subjects with moderate hepatic impairment. However, if only 5 mg BID is approved, a reduced tofacitinib dose of 5 mg QD is recommended in these subjects.
- Tofacitinib was not evaluated in patients with severe hepatic impairment because of the risk of immunosuppression in patients who are already at risk of infection from their hepatic disease (for the reason that a significant portion of tofacitinib is cleared through hepatic metabolism). Therefore, tofacitinib is not recommended in patients with severe hepatic impairment

Drug-Drug Interaction (DDI)

Effect of coadministered drugs on tofacitinib exposure

- Tofacitinib coadministration with a strong CYP3A inhibitor, ketoconazole, increased the mean tofacitinib AUC (90%CI) by 103% (91%, 116%) and C_{max} by 16% (5%, 29%). If both 5 and 10 mg BID doses are approved, tofacitinib dose should not exceed 5 mg BID when it is coadministered with strong CYP3A4 inhibitors. However, if only 5 mg BID is approved, a reduced tofacitinib dose of 5 mg QD is recommended when coadministered with strong CYP3A4 inhibitors
- Coadministration with a moderate CYP3A4 and strong CYP2C19 inhibitor, fluconazole, increased mean tofacitinib AUC (90%CI) by 79% (64%, 96%) and C_{max} by 27% (12%, 44%). If both 5 and 10 mg BID doses are approved, tofacitinib dose should not exceed 5 mg BID when it is coadministered with moderate CYP3A4 and strong CYP2C19 inhibitors. However, if only 5 mg BID is approved, a reduced tofacitinib dose of 5 mg QD is recommended for coadministration with moderate CYP3A4 and strong CYP2C19 inhibitors
- Tofacitinib coadministration with a strong CYP3A inducer, rifampin, resulted in substantial decreases in mean tofacitinib AUC (90%CI) by -84% (-86%, -82%) and in C_{max} by -74% (-77%, -69%). Coadministration with rifampin is not recommended because that will result in inefficacious concentrations of tofacitinib
- Coadministration with tacrolimus, a CYP3A substrate with narrow therapeutic index, increased mean (90%CI) tofacitinib AUC (90%CI) by 21% (13%, 30%) and decreased C_{max} by -9% (-17%, -1%). However, because of potential for pharmacodynamic drug interaction (immunosuppressive drug effects from both drugs), tofacitinib coadministration with tacrolimus is not recommended

- Coadministration with cyclosporine, a CYP3A substrate with narrow therapeutic index and also an inhibitor of P-gp increased mean (90%CI) tofacitinib AUC (90%CI) by 73% (62%, 85%) and decreased C_{max} by -17% (-29%, -3%). However, because of potential for pharmacodynamic drug interaction (immunosuppressive drug effects from both drugs), tofacitinib coadministration with cyclosporine is not recommended
- Coadministration with methotrexate, had no significant effect on mean (90%CI) tofacitinib exposure with geometric mean ratio and 90% CI for AUC of 103% (99%, 107%) and for C_{max} of 103% (94%, 112%). No dose adjustment recommended for tofacitinib when coadministered with methotrexate

Effect of tofacitinib on exposure of coadministered drugs

- Concomitant use of oral contraceptives (OC) with tofacitinib did not have any significant effect on plasma levels of ethinyloestradiol with geometric mean ratio (90%CI) for comparison with vs. without tofacitinib were, for AUC, 107% (99%, 115%), and for C_{max}, 90% (82%, 98%), and on plasma levels of levonorgestrel with geometric mean ratio (90%CI) for comparison of with vs. without tofacitinib were for AUC of 101% (95%, 107%) and for C_{max} of 112% (105%, 120%). No dose adjustment recommended for OC when coadministered with tofacitinib
- Concomitant use with tofacitinib had no substantial effect on the exposure of midazolam, a sensitive CYP3A substrate, with geometric mean ratio (90%CI) with vs. without tofacitinib were for AUC of 104% (96%, 113%) and for C_{max} of 102% (96%, 109%). No dose adjustment recommended for CYP3A substrates when coadministered with tofacitinib
- Concomitant use of tofacitinib and methotrexate, decreases mean (90% CI) methotrexate AUC by -10% (-23%, 4%) and C_{max} by -13% (-24%, 0%). No dose adjustment recommended for methotrexate when coadministered with tofacitinib

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

Thirteen in vitro studies using human biomaterials were conducted and are listed Table 1.

Table 1: Tofacitinib (CP-690,550) In Vitro Studies Using Human Biomaterials

Objective	Study Number
Plasma Protein Binding of CP-690,550 in Mouse, Rat, Dog, Monkey and Human	DM2001-690550-018
Protein Binding of CP-690,550 in Human Serum Albumin and α1-Acid Glycoprotein	DM2002-690550-025
Blood to Plasma Concentration Ratio of CP-690550 in Rat, Monkey and Human Whole Blood	CP-690550_18Feb11_055956
Identification of In vitro Metabolites of CP-690,550 in Human Liver Microsomes and Recombinant CYP450 isoforms	DM2004-690550-046
Identification of Human CYP450 Isoforms Responsible for In Vitro Metabolism of CP-690,550	DM2007-690550-067
Effect of CP-690,550 on Human Drug Metabolizing Enzymes In vitro	DM2001-690550-020
Potential for CP-690,550 to induce CYP3A4 And CYP1A2 In Human Hepatocytes	DM2007-(b) (4)-001
Evaluation of CP-690,550 as Substrate for P-Glycoprotein	XT088024(b) (4)
Potential for CP-690,550 to Inhibit P-Glycoprotein	(b) (4)10/17Oct08/060532
Evaluation of CP-690,550 as Substrate for BCRP	CP-690550_15Oct10_175813
Potential for CP-690,550 to Inhibit OCT2	CP-690,550/09Jun08/135323
Potential for CP-690,550 to Inhibit OATP 1B1	CP-690550_28Jul10_192119
Potential for CP-690,550 to Inhibit OATP 1B3	CP-690550_02Aug10_095440

BCRP – Breast cancer resistance protein; OATP – Organic Anion Transport Protein; OCT – Organic Cation Transporter

(Source –Table 1, Section 2.7.2, Summary of Clinical Pharmacology Studies)

Studies in Healthy Subjects

Nine Phase 1 studies characterized the single and/or multiple-dose PK of tofacitinib.

- Single-dose escalation (First-in-Human) for tofacitinib was studied in healthy volunteers in Study A3921002.
- Multiple-dose escalation and tolerability was evaluated in Study A3921003 in subjects with medically stable psoriasis.
- Study A3921005 was conducted in healthy volunteers to evaluate the bioavailability of a tablet formulation of tofacitinib relative to the OPC formulation.
- The effect of food on tofacitinib PK was assessed in Study A3921005 and later repeated with the proposed commercial tablet in Study A3921076.
- Study A3921010 evaluated the metabolic profile and routes of excretion of radiolabeled tofacitinib (i.e., [^{14}C]CP-690,550) in healthy male subjects.
- Study A3921077 was conducted in healthy volunteers to determine the absolute bioavailability of tofacitinib.
- Study A3921075 was conducted to establish bioequivalence between the Phase 2B, Phase 3 and the commercial tablet formulations.
- Study A3921036 evaluated the PK of tofacitinib in Japanese and Western subjects
- Study A3921065 examined the PK of tofacitinib in Chinese subjects.

Studies Evaluating the Impact of Change Renal and Hepatic Function or Impact on Renal Function

Three clinical studies evaluated the PK of tofacitinib in subjects with renal or hepatic impairment.

- The PK and dialyzability of tofacitinib were evaluated in subjects with End Stage Renal Disease (ESRD) in Study A3921004.

- Study A3921006 investigated the PK of tofacitinib in subjects with mild, moderate and severe renal impairment.
- Study A3921033 evaluated the effect of 14 days treatment with tofacitinib on renal function (glomerular filtration rate (GFR)) in healthy volunteers
- Study A3921015 examined the PK of tofacitinib in subjects with mild and moderate hepatic impairment. Subjects with severe hepatic impairment were not evaluated.

Studies of Drug-Drug Interactions
Seven clinical studies evaluated drug-drug interactions with tofacitinib.
- The effect of other drugs on the PK of tofacitinib was evaluated in the following studies: methotrexate (A3921013), fluconazole (A3921014), tacrolimus and cyclosporine (A3921020), ketoconazole (A3921054) and rifampin (A3921056).
- The effect of tofacitinib on the PK of other drugs was evaluated in the following studies: midazolam (A3921059), oral contraceptives (A3921071) and methotrexate (A3921013).

Phase 2 Dose-Ranging Studies
Five dose ranging studies evaluated more than one dose levels of tofacitinib.
Global studies
- Study A3921019 was a 6-week, double-blind, placebo-controlled, parallel group, monotherapy study
- Study A3921025 was a 24-week, double-blind, placebo-controlled, parallel group study in patients receiving background methotrexate
- Study A3921035 was a 24-week, double-blind, placebo- and active-controlled, parallel group, monotherapy study

Studies in Japanese Patients
- Study A3921039 was a 12-week, double-blind, placebo-controlled, parallel group, study in Japanese patients receiving background methotrexate
- Study A3921040 was a 12-week, double-blind, placebo-controlled, parallel group, monotherapy study in Japanese patients

Population Pharmacokinetic Studies
Population pharmacokinetic analysis used tofacitinib plasma concentration-time data from five Phase 2 studies in RA patients.

Phase 3 Study
Trough concentrations were collected over 12 months in the Phase 3 study A3921064

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?

Tofacitinib is a small molecule drug. Its structure is shown in Figure 1 and physico-chemical properties are listed in Table 2.

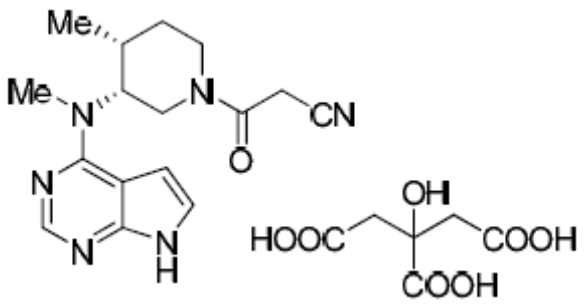


Figure 1: Molecular structure of tofacitinib

Table 2: Tofacitinib physical chemical properties

Molecular Formula	$C_{16}H_{20}N_6O \bullet C_6H_8O_7$
Molecular Weight	504.5 g/mol (312.4 g/mol as free base)
Physical State	Powder
Polymorphism	There is only (b) (4) of CP-690,550-10 designated as (b) (4)
Dissociation Constants	$pK_a = 5.07$
Solubility	• Water: 2.9 mg/mL (freely soluble in water) • 3.48 - >28 mg/mL in aqueous solution of pH 1 – 3.9 • 0.20 – 0.59 mg/mL in aqueous solution of pH 4.53 – >8 • Solubility decreases with increase in pH
Partition Coefficient	Log P=1.15 of the neutral form (free base) Average partition coefficient = 14.3 at pH 7.3

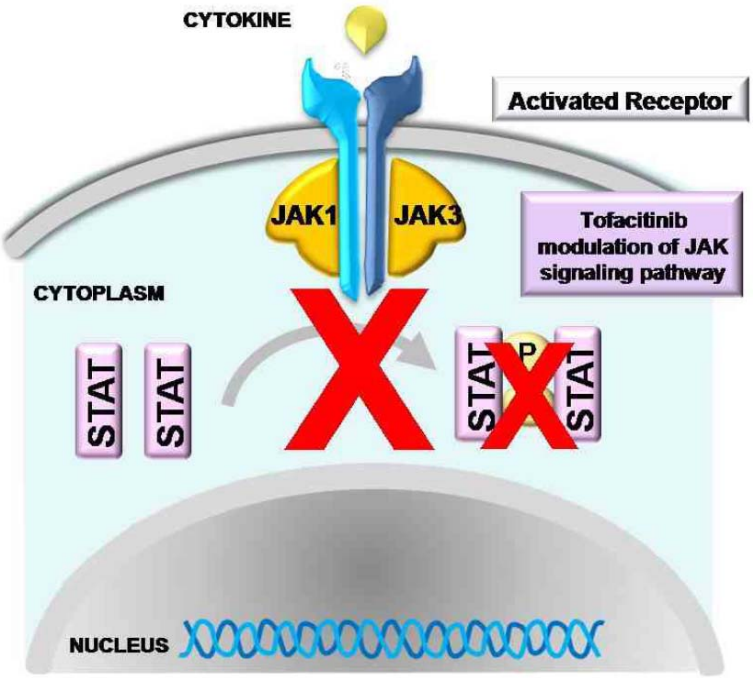
Drug Product

Tofacitinib is supplied for oral administration in two strengths: 5 mg white to off-white round and 10 mg blue round immediate-release film-coated tablets. The to-be-marketed formulation is different from the formulation tested in Phase 3 clinical trials with respect to the amount of excipients and coating (see 2.8.2 for more details).

2.2.2 What are the proposed mechanism of action and therapeutic indications?

Tofacitinib is proposed to act as an inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In cell assays, tofacitinib preferentially inhibits JAK1 and/or JAK3 mediated signaling. Inhibition of JAK1 and JAK3 by tofacitinib may potentially block signaling through cytokines such as IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, which in turn may suppress the immune system (Figure 2). Tofacitinib is also being evaluated in other diseases in which lymphocyte activation/proliferation plays a pathogenic role.

The proposed indication is treatment of rheumatoid arthritis in patients with moderate to severe disease who have an inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs).



JAK=Janus kinase; P=phosphate; STAT=signal transducer and activator of transcription.

- Tofacitinib binds in the catalytic cleft in the kinase domain of JAKs
- Tofacitinib modulates the JAK signaling pathways at the point of JAK, preventing the phosphorylation and activation of signal transducer and activators of transcription (STAT).
- Inhibition of JAK1/JAK3 is expected to block signaling through the common γc -containing cytokine receptors, including those for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21; these cytokines are integral to lymphocyte activation, proliferation and function and may thus result in modulation of multiple aspects of the immune response.
- In addition, inhibition of JAK1 may lead to some modulation of additional cytokine receptor signaling, including IFN-α, IFN-β and IL-6

Figure 2: Tofacitinib mechanism of action
(Source – Figure 1, Pfizer Advisory Committee Meeting Briefing Package)

2.2.3 What are the proposed dosages and routes of administration?

The proposed starting dose is 5 mg BID to be given orally. In some patients, doses can be increased to 10 mg BID based on clinical response.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

The drugs which are approved for treatment of RA in the US can be classified into three general classes:

(a) *Nonsteroidal anti-inflammatory drugs (NSAIDs)*
-improves symptoms

- Salicylates: acetyl salicylic acid, diflunisal, magnesium salicylate
- Arylalkanoic acids: diclofenac, indomethacin, etodolac, sulindac, tolmetin
- 2-Arylpropionic acids: ibuprofen, naproxen, ketoprofen, oxaprozin

- N-Arylanthranilic acids: mefenamic acid, flufenamic acid, meclofenamic acid
- Pyrazolidine derivatives: phenylbutazone, metamizole, phenazone
- Oxicams: piroxicam, meloxicam
- Sulfonilides: nimesulide

(b) *Corticosteroids*
-Combination of low-dose glucocorticoids with disease modifying anti-rheumatic drugs (DMARDs) increases efficacy, including slowing of structural damage, and treatment-related toxicity

(c) *DMARDs (Non-biologic and Biologic)*
-improves symptoms and reduces or prevents joint structural damage

- Non-biologic: Methotrexate, Leflunomide, Cyclosporine A, Azathioprine etc.
- Biologic
  - TNF-inhibitors: Adalimumab, Certolizumab, Golimumab, Infliximab, Etanercept etc.
  - Mechanisms other than TNF-inhibitors: Abatacept, Rituximab, Tocilizumab, Anakinra etc.

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 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?

Sponsor has used ACR20, ACR50, ACR70 and DAS28-3(CRP) as the primary endpoints for signs and symptoms in all key efficacy studies. Use of ACR and DAS28 as indicators of improvement in signs and symptoms is widely accepted and is recommended by the American College of Rheumatology (ACR). These endpoints have also been used by the FDA for approval of other drugs in Rheumatology.

Among clinical pharmacology studies, these endpoints were measured in the 5 dose-ranging studies conducted by the sponsor.

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?

Please refer to pharmacometrics review (response 1.1.2).

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

Please refer to pharmacometrics review (response 1.1.3).

2.4.3 Does this drug prolong QT/QTc Interval?

QT effect was evaluated in a randomized, blinded, crossover, single-dose study, in which 60 healthy subjects received a supra-therapeutic tofacitinib dose of 100 mg, placebo, and moxifloxacin 400 mg. The washout duration between treatment periods was 7 days. No significant QT prolongation effect was detected at the tested 100 mg tofacitinib dose. The largest upper bounds of the 2-sided 90% CI for the mean difference between CP-690,550 100 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guideline. For further details refer to QT/IRT review of the study A3921028 submitted under IND (b) (4)

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Please refer to pharmacometrics review (response 1.1.4).

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

In a single dose study in healthy adults, tofacitinib PK was characterized for doses ranging from 0.3 mg to 100 mg. Mean plasma concentration-time profile is shown in Figure 3. Following oral administration, maximum plasma concentration of CP-690,550 was reached by 0.5 to 1 hour (i.e., T_{max}). The terminal half-life after single dose ranged from 2.3-3.1 hrs. CP-690,550 appears to follow mono-exponential disposition kinetics with parallel terminal slopes. PK parameters for different dose levels are summarized in Table 3.

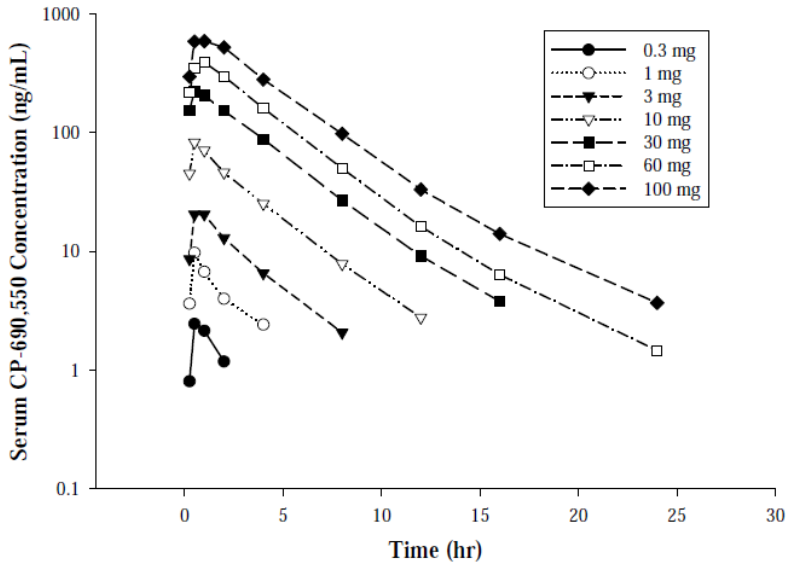


Figure 3: Mean Serum CP-690,550 Concentrations vs Times Following Administration of a Single Oral OPC Dose of CP-690,550 to Fasted Healthy Subjects
(Source – Figure A, Study A3921002 report)

Table 3: Mean (SD) Pharmacokinetic Parameters of CP-690,550 Following Administration of a Single Oral Dose of CP-690,550 OPC to Fasted Healthy Subjects

Dose group	$AUC_{0\text{-}Tlast}$ (ng*hr/mL)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	Cmax (ng/mL)	Tmax† (hr)	$T_{1/2}$ (hr)
0.1 mg N=8	0.158 (0.01)	NC	1.27 (0.082)	0.5 (0.5 – 0.5)	NC
0.3 mg N=8	3.91 (2.07)	NC	2.65 (0.619)	0.5 (0.5 – 1)	NC
1 mg N=8	19.2 (6.54)	NC	10.5 (2.28)	0.5 (0.5 – 1)	NC
3 mg N=8	69.5 (13.4)	75.5 (14)	21.8 (3.04)	0.5 (0.5 – 1)	2.31 (0.348)
10 mg N=8	283 (80.3)	289 (81.5)	88 (10.2)	0.5 (0.25 – 1)	2.61 (0.633)
30 mg N=9	933 (176)	938 (175)	240 (44.5)	0.5 (0.25 – 2)	2.72 (0.576)
60 mg N=8	1710 (435)	1720 (438)	408 (97.7)	1 (0.5 – 1)	2.68 (0.555)
100 mg N=7	2980 (709)	2990 (716)	638 (118)	0.5 (0.5 – 2)	3.07 (0.571)

†Median and Range are reported for Tmax
NC = Not Calculated, SD = Standard Deviation
(Source – Table Q, Study A3921002 report)

Multiple dose PK

Multiple dose PK of tofacitinib was characterized in medically stable subjects with psoriasis. Tofacitinib PK after multiple doses was consistent with the single dose PK. T_{max} was reached within 0.5-1 hr, mean apparent terminal $t_{1/2}$ ranged from 2.3 – 4.3 hrs. Accumulation after multiple doses was minimal. Except for 30mg dose, mean accumulation ratio for all other doses ranged from 0.98 to 1.22, which was as expected based on short half-life and BID dosing regimen. Mean plasma PK profiles are shown in Figure 4 and summary PK parameters are listed in Table 4. From other studies, measurement of trough concentrations indicated that steady-state was achieved within 24-48 hrs after initiating repeat dosing.

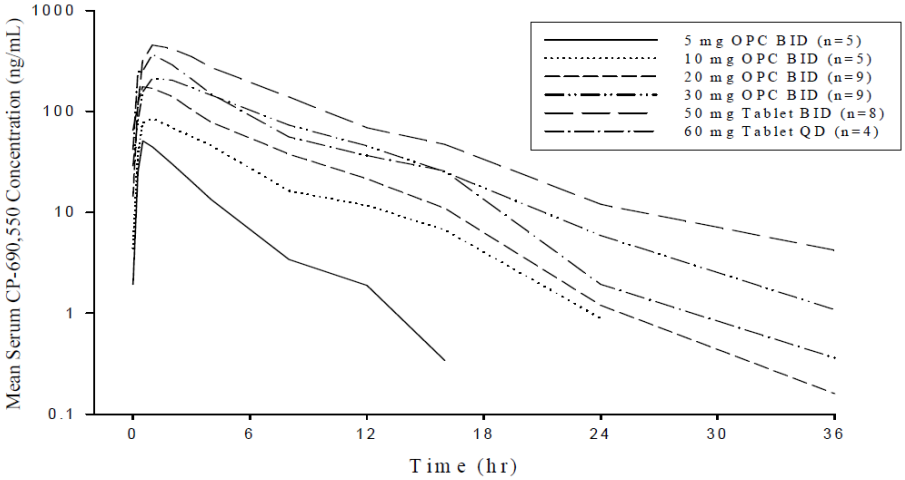


Figure 4: Mean Serum CP-690,550 Concentrations Versus Time on Day 14 Following Multiple Oral Dosing with CP-690,550 in Medically Stable Subjects with Psoriasis
(Source – Figure 1, Study A3921003 report)

Table 4: Arithmetic Mean (SD) CP-690,550 Serum Pharmacokinetic Parameters on Days 1 and 14 Following Multiple Oral Dosing with CP-690,550 in Medically Stable Subjects with Psoriasis

Cohort	C_{max} ng/mL		$AUC_{0\text{-}tau}$ ng·h/mL		R_{ac}	T_{max} h[a]		t1/2 hr
	Day 1	Day 14	Day 1	Day 14	Day 14/Day 1	Day 1	Day 14	Day 14
5 mg OPC BID (n=5)	48.3 (24.5)	50.9 (21.2)	161 (86.1)	154 (80.3)	0.974 (0.181)	0.50 (0.25-1.00)	0.50 (0.50-0.50)	2.26 (0.518)
10 mg OPC BID (n=5)	90.5 (20.4)	87.7 (13.2)	349 (34.7)	422 (49.5)	1.22 (0.203)	0.50 (0.50-1.00)	1.00 (0.50-1.00)	3.93 (0.456)
20 mg OPC BID (n=9)	212 (62.3)	194 (53.9)	732 (232)	850 (216)	1.22 (0.389)	0.50 (0.25-2.00)	0.50 (0.25-2.00)	3.61 (0.548)
30 mg OPC BID (n=9)	180 (53.1)	225 (43.9)	860 (235)	1350 (308)	1.62 (0.343)	0.50 (0.50-3.00)	1.00 (0.50-4.00)	4.30 (0.884)
60 mg Tablet QD (n=9[b])	429 (99.1)	403[b] (133)	1720 (453)	1780[b] (501)	1.14[b] (0.176)	1.00 (0.50-2.00)	1.00[b] (0.50-2.00)	NR[b]
50 mg Tablet BID (n=8)	457 (88.2)	568 (205)	2120 (837)	2600 (1580)	1.16 (0.270)	1.00 (0.50-3.00)	1.00 (0.50-2.00)	3.92 (1.36)

[a] Median (Range) reported for tmax
[b] Only 4 subjects had calculable data on Day 14 in the 60 mg Tablet QD cohort
NR: Not reported due to insufficient data
Source: Tables 5.2.1, 5.2.4 – 5.2.6
(Source – Table 19, Study A3921003 report)

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

In a sponsor reported meta-analysis of non-compartmental PK parameters from healthy subjects across 16 Phase 1 studies, the pooled geometric mean estimate of CL/F was 34.9 L/h. While the mean CL/F estimate, calculated based on population PK analysis, for a typical RA patient was 18.4 L/h. Although derived using different methods, clearance in RA patients was approximately 43% lower relative to healthy subjects. This may be attributed to down-regulation of cytochrome P450 enzymes in RA patients by inflammation stimuli including cytokines such as IL-6 and TNF-alpha[1]. Geometric mean estimate of half-life in healthy subjects based on sponsor reported pooled meta-analysis was approximately 3 hrs and the mean half-life in a typical RA patient based on population PK analysis was approximately 3.6 hrs.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Summary of inter- and intra-subject variability as reported by the sponsor is presented in Table 5. Tofacitinib exhibits moderate inter- and intra-subject variability with similar or slightly higher inter-subject variability in RA patients compared to healthy subjects. Observed intra-subject variability in AUC and C_{max} was similar between healthy subjects (i.e., 5-7%) and RA patients from DDI study (i.e., 5.5%), but the variability in AUC projected based on intra-occasion variability in bioavailability in the population PK analysis was relatively higher (i.e., ~23%).

Sponsor reported plot of percent deviation of individual AUC and Cmax values from group means in Phase 1 studies (Figure 5) show that majority of AUC and Cmax values deviate less than 50% from individual study group means.

Table 5: Variability Estimates (%CV) for Tofacitinib Exposure in Healthy Subjects and RA Patients

Population	Inter-subject variability (%CV)		Intra-subject variability (%CV)	
	AUC(0-∞)	Cmax	AUC(0-∞)	Cmax
Healthy Subjects (Biopharmaceutics Studies)[a]	19-26%	11-28%	5-7%	12-25%
RA Patients (Population PK)[b]	26.6%[d]	NC	23.0%[e]	NC
RA Patients (DDI Study with Methotrexate)[c]	32.3%	21.0%	5.5%	12.4%

Source:
[a] - Clinical study reports Section 11, Item 11 Table 3.1 and 3.2 for A3921005, Table 16.1.9.2.1 for A3921075, Table 16.1.9.2.1 for A3921076, Table 16.1.9.2.1 for A3921077;
[b] PMAR-00178 Table 11;
[c] - Clinical study reportTable A10.2.1 and A.10.2.2 for A3921013;
[d] - inter-individual variability in CL/F
[e] - inter-occasion variability in F

(Source –Table 35, Section 2.7.2, Summary of Clinical Pharmacology Studies)

[1] Aitken, A.E., Richardson, T.A. & Morgan, E.T. Regulation of drug-metabolizing enzymes and transporters in inflammation. *Annu. Rev. Pharmacol. Toxicol.* **46**, 123–149 (2006).
Kulmatycki, K.M. & Jamali, F. Drug disease interactions: role of inflammatory mediators in disease and variability in drug response. *J. Pharm. Pharm. Sci.* **8**, 602–625 (2005)

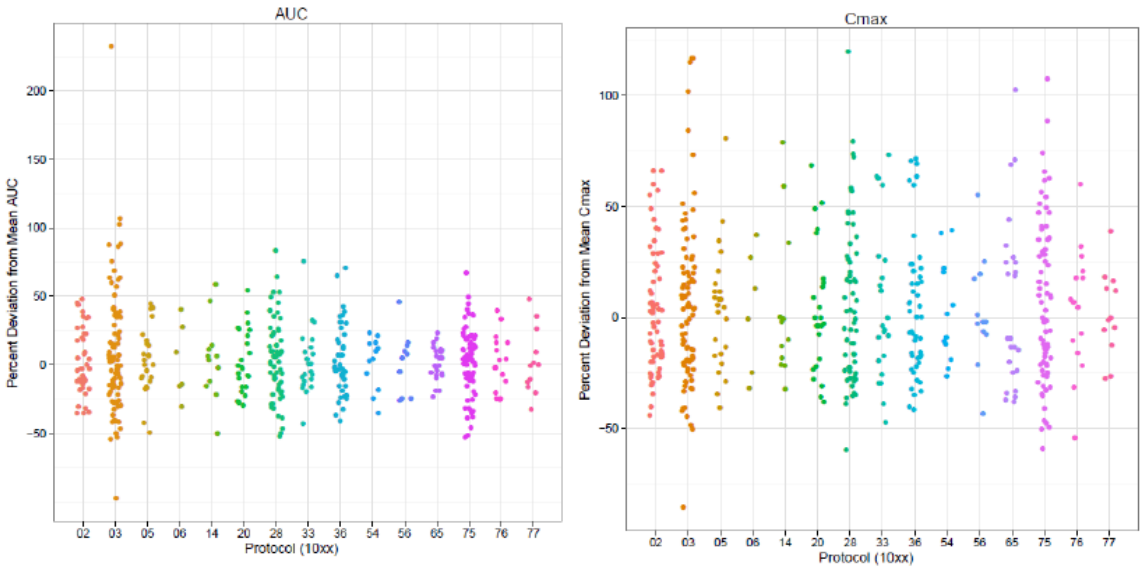


Figure 5: Percent deviation of individual tofacitinib AUC and Cmax values from group means following oral administration in healthy subjects
(Source – Figure 20, Section 2.7.2, Summary of Clinical Pharmacology Studies)

2.5.4 What are the characteristics of drug absorption?

Tofacitinib absolute oral bioavailability following oral administration was ~74%. In single- and multiple-dose studies, maximum plasma concentrations were reached within 0.5-1 hr after oral administration. In-vitro studies using transfected MDCK cells, demonstrated that tofacitinib is a substrate of P-gp (ABCB1), but not the BCRP (ABCG2) efflux transporter (see sections 2.7.3 and 2.7.4). However, because of high oral bioavailability, inhibition of P-gp will likely have a minimal effect on the extent of oral absorption. The rate of absorption was reduced when tofacitinib was given with food (median t_{max} increased from 0.5 to 2 hours and C_{max} was reduced by about 32% (95% CI: 23.4 to 41.6%)), but there was no effect of food on the extent of absorption (see section 2.8.3).

2.5.5 What are the characteristics of drug distribution?

Following IV dosing, the apparent steady-state volume of distribution (V_{ss}) of tofacitinib was estimated to be 87 L, suggesting distribution into tissues. In vitro studies determined low to moderate plasma protein binding for tofacitinib with the fraction unbound to (fu) in humans to be 0.61. Tofacitinib was shown to bind moderately to human serum albumin (fu = 0.51) but does not bind to alpha1-acid glycoprotein (fu~1). In vitro studies indicated relatively equal distribution of tofacitinib between red blood cells and plasma with blood-to-plasma concentration ratio of 1.2 at 1 μM concentration.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Majority of the orally administered drug was recovered in urine; however, only 29% is recovered in form of parent drug and rest was in form of metabolites. Therefore, hepatic metabolism is the major route of elimination for tofacitinib. Scheme showing disposition of tofacitinib following oral administration based on mass balance study and absolute bioavailability study is shown in Figure 6.

Table 6: Percentage of Dose Excreted in Urine and Feces over 192 Hours by Male Subjects Following Oral Administration of a Single 50 mg Dose of [14C]CP-690,550

Subject #	Subject ID	Urine	Feces	Total*
1	10011003	80.5	15.8	96.4
2	10011007	73.6	14.4	88.0
3	10011009	79.5	13.6	93.1
4	10011010	83.2	15.5	98.6
5	10011012	80.0	12.9	92.9
6	10011017	83.6	10.7	94.3
Mean		80.1	13.8	93.9
SD		3.6	1.9	3.6

(Source – Table 7, Study A3921010 report)

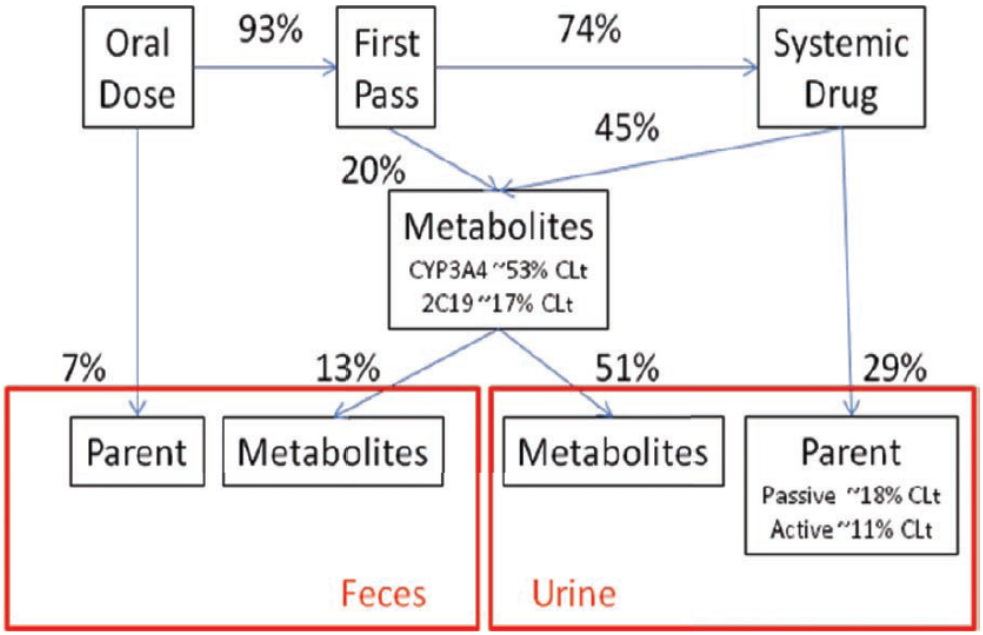


Figure 6: Mass Balance Model for Tofacitinib Following Oral Administration based on Mass Balance and Absolute Bioavailability Study
(Source – Figure 18, Section 2.7.2, Summary of Clinical Pharmacology Studies)

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

In plasma, approximately 69% of the total circulating radioactivity was accounted for by unchanged drug (CP-690,550 in Table 7) with the rest circulating in form of metabolites, each accounting for less than 8% of total radioactivity (Table 7).

Table 7: Percentage of Circulating Metabolites of CP-690,550 in Male Subjects Following Oral Administration of a Single 50 mg Dose of [14C]CP-690,55

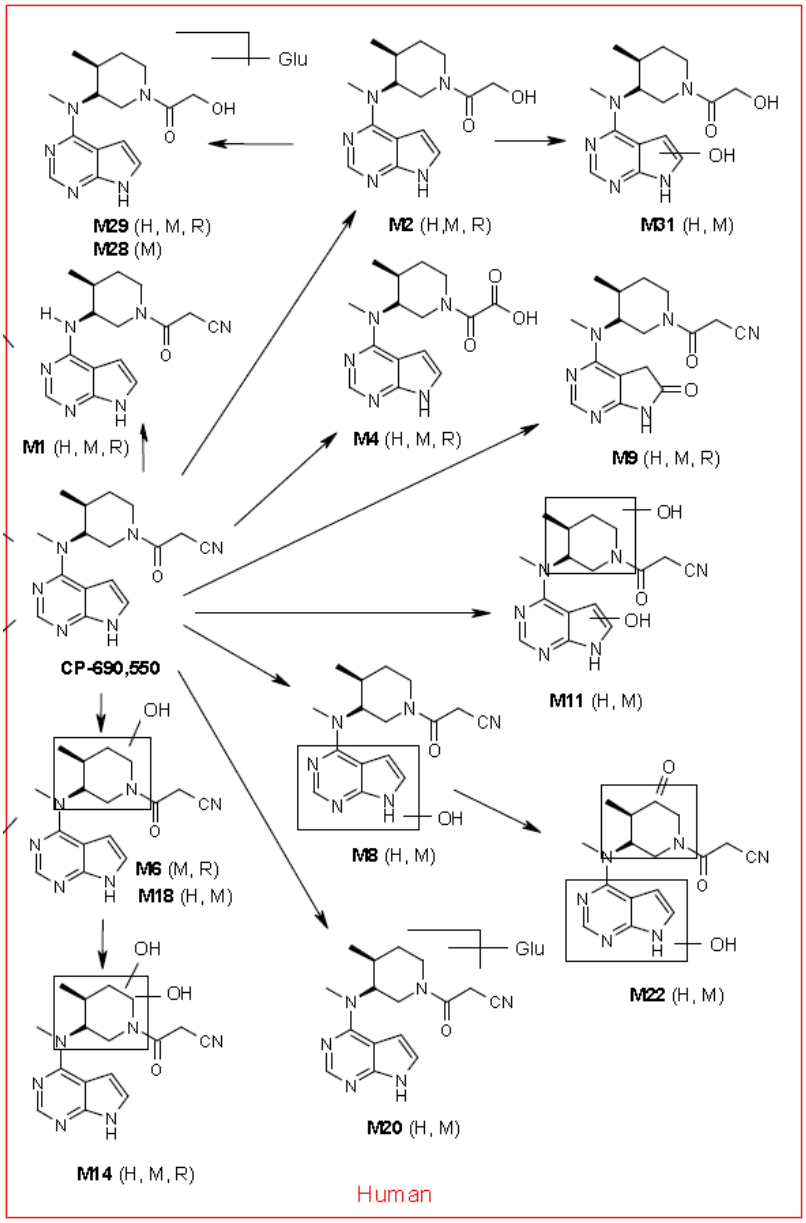
Metabolites	m/z	Ret. Time (min)	Percent of Dose							
			Subject #							
			1	2	3	4	5	6	Mean	SD
M14	345	8.3	3.2	0.7	1.1	4.5	3.3	6.2	3.2	2.1
M4	318	12.4	4.4	5.3	1.4	5.5	2.6	4.5	3.9	1.6
M20, M11, M29	489, 345, 480	15.1	4.8	8.0	4.7	7.5	5.8	6.6	6.2	1.4
M1, M2	299, 304	17.6	0.8	7.3	7.4	7.9	10.4	10.9	7.4	3.6
CP-690,550	313	20.8	77.5	69.5	77.1	57.4	73.8	61.1	69.4	8.5
M9	329	26.4	1.6	1.2	0.6	0.5	ND	ND	1.0	0.5

ND = Not detected

(Source – Table 9, Study A3921010 report)

2.5.8 What are the characteristics of drug metabolism?

The proposed metabolic pathway for tofacitinib is shown in Figure 7. Both in vitro and in vivo studies indicate that tofacitinib or CP-690,550 is extensively metabolized. Primary metabolic pathways of CP-690,550 include oxidation of the pyrrolopyrimidine ring (M8 and M9), oxidation of the piperidine ring (M18), and oxidation of the piperidine ring side chain (M2 and M4). The other metabolites were due to combinations of these primary metabolic pathways. Sponsor reported that all metabolites have or are predicted to have ≤10 % of the potency of CP-690,550 for JAK1/3 inhibition.



(H)-Human; (M)-Monkey; (R) –Rat

Note – Not all of the metabolites from biotransformation of tofacitinib in rat and monkey are shown in the figure. Only the metabolites which are common with humans are shown.

Figure 7: Proposed Biotransformation Pathways for CP-690,550 in Human (H) Plasma, Urine and Feces

(Source – adapted from Figure 3, Section 2.6.4, Written Summary of Non-Clinical Pharmacokinetics)

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

In vitro studies determined that tofacitinib is not a substrate of BCRP. In a preclinical study in bile duct cannulated male monkeys, about 25% of the total administered drug was recovered in bile. Unchanged drug accounted for only 0.3% of the dose in bile and the rest was recovered in form of glucuronide metabolites (M23, M26, M29) and other

metabolite (M25).

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

The available plasma concentration-time profile information does not suggest enterohepatic recirculation for tofacitinib.

2.5.11 What are the characteristics of drug excretion in urine?

Mass balance study suggested that renal clearance constitutes approximately 30% of the total clearance of CP-690,550. Estimates of renal clearance (CLr) of CP-690,550 were obtained in healthy subjects in Phase 1 studies. The overall mean estimate of CLr from these studies in the treatment groups was 127 mL/min, which when adjusted for protein binding (fu of 0.61) exceeds GFR, suggesting an additional contribution from active tubular secretion.

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

Tofacitinib AUC and Cmax increased in dose proportional manner with increase in dose from 1 to 100 mg and 0.3 to 100 mg, respectively, based on PK parameters from single dose PK study (Figure 8). The point estimate of slope for AUC vs. dose relationship after single-dose is close to 1 and 90% CI includes 1, suggesting dose-proportionality in the dose range from 1 to 100 mg (Table 7). The point estimate of slope for C_{max} vs. dose relationship after single-dose is also close to 1 but 90% CI does not include 1, suggesting approximately dose-proportional relationship in dose range from 0.3 to 100 mg (Table 7).

After multiple-dose, slopes for relationship of AUC_{tau} and $C_{max,ss}$ is also close to 1, indicating that dose-proportionality is retained after repeat dosing in the dose range of 5 to 60 mg (Figure 9 and Table 8).

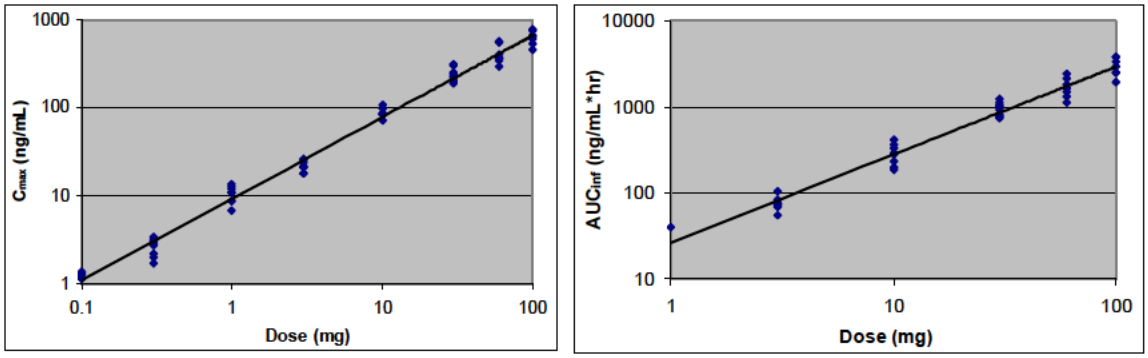


Figure 8: Assessment of dose proportionality for C_{max} and AUC after single-dose (log-scale)

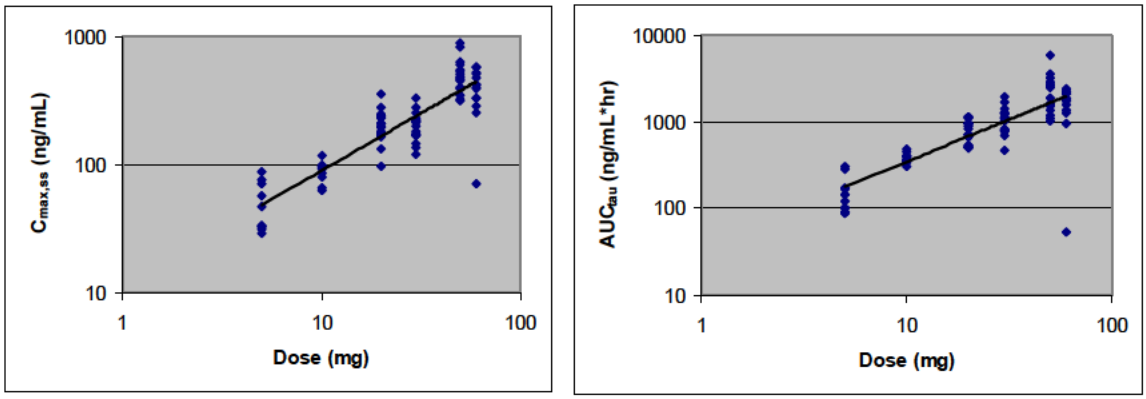


Figure 9: Assessment of dose proportionality for $C_{max,ss}$ and AUC_{tau} after multiple-dose (log-scale)

Table 8: Point estimate and 90% CI for slope of power relationship* between Dose and PK metrics

	Parameters	Dose Range	Slope	90% CI
Single dose	C_{max} (ng/mL)	0.3 – 100 mg	0.93	0.91, 0.95
	AUC_{inf} (ng/mL*hr)	1 – 100 mg	1.02	0.97, 1.07
Multiple dose	$C_{max,ss}$ (ng/mL)	5 – 60 mg	0.90	0.81, 0.98
	AUC_{tau} (ng/mL*hr)	5 – 60 mg	0.97	0.85, 1.10

$$* \text{ (PK metrics)} = \text{Intercept} \cdot (\text{Dose})^{\text{Slope}}$$

2.5.13 How do the PK parameters change with time following chronic dosing?

In population PK analysis, a separate CL/F parameter was estimated for each study occasion. Within each study, the estimates of typical CL/F across different occasions (ranging between Day 0 and Week 16) differed by less than 13% (see Pharmacometrics review section 3, Figure 42), indicating no time dependency in CL/F. Trough (pre-dose) concentrations measured over a 12-month period in a Phase 3 study also did not show evidence of time-dependency (Table 9).

Table 9: Descriptive Statistics of Pre-dose Plasma Concentrations (ng/mL) of Tofacitinib in Phase 3 Study A3921064

Dose	Month	N[a]	Arithmetic Mean	Geometric Mean	% CV[b]	Median	Minimum	Maximum
5 mg BID	3	177	6.80	3.48	156	3.23	0.183	73.1
	6	167	7.19	3.84	143	3.86	0.249	64.0
	12	145	6.47	3.08	156	3.33	0.106	67.0
10 mg BID	3	169	13.6	6.62	135	7.29	0.105	110
	6	163	16.1	7.58	211	7.57	0.150	334
	12	148	13.0	6.02	153	6.58	0.100	135

Source: CSR A3921064 Table 14.4.4.3
[a] Number of subjects; concentrations below the LLOQ were excluded from this summary
[b] % coefficient of variation
(Source – Table 34, Section 2.7.2, Summary of Clinical Pharmacology Studies)

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

In clinical PK studies tofacitinib was given in two times a day dosing regimen (possibly 12 hours apart). It was observed that PK after single-dose was comparable with PK after multiple-dose, which may suggest that circadian rhythm may not have any effect on tofacitinib PK.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Effect of intrinsic factors on exposure of tofacitinib was assessed in population PK analysis. Please see discussion under heading "assessment of impact of covariates on AUC_{ss} and $C_{max,ss}$ metrics" in section 3 of pharmacometrics review, Figure 44.

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?

Please see pharmacometrics review as stated in response 2.6.1.

2.6.2.1 Severity of Disease State

Not assessed.

2.6.2.2 Body Weight

Please see pharmacometrics review as stated in response 2.6.1.

2.6.2.3 Elderly

Please see pharmacometrics review as stated in response 2.6.1.

2.6.2.4 Pediatric Patients

Safety and effectiveness of tofacitinib in pediatric patients has not been evaluated. A waiver for < 2 years age and a deferral for age 2 to 17 years 11 months is to be discussed in PeRC on June 20, 2012. Evaluation in age 2 to 17 years 11 months is deferred until complete evaluation of safety and benefit-risk profile. However, sponsor's proposal for age 2 to 17 years 11 months includes a PK study and 3 efficacy and safety studies.

2.6.2.5 Race/Ethnicity

Please see pharmacometrics review as stated in response 2.6.1.

In addition, PK between Western and Japanese subjects was compared in a dedicated study. There was no clinically meaningful difference in single-dose PK between these two ethnic groups (Figure 10 and Table 10). PK for Japanese subjects after single-dose or multiple-dose was similar.

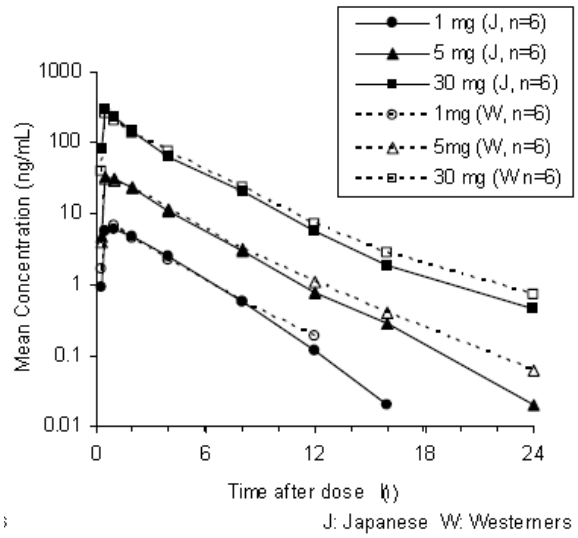


Figure 10: Mean plasma concentration of CP-690,550 following single oral dose administration in healthy Japanese and Western subjects (semi-log scale)

(Source – Figure 1, Study A3921036 report)

Table 10: Mean PK parameters of CP-690,550 following administration of single doses in healthy Japanese and Western subjects

		Japanese			Westerners		
		1 mg	5 mg	30 mg	1 mg	5 mg	30 mg
	n	6	6	6	6	6	6
C_{max} (ng/mL)	Geometric Mean	7.32	41.3	315	7.36	34.9	265
	%CV	14	35	25	22	27	18
	J/W (%)[a]	99.5	118	119	na	na	na
	90%CI	(81.1, 122)	(87.4, 161)	(93.0, 151)	na	na	na
AUC_{inf} (ng·h/mL)	Geometric Mean	22.0	111	754	22.8	119	788
	%CV	28	22	26	11	14	16
	J/W (%)[a]	96.6	93.5	95.6	na	na	na
	90%CI	(76.7, 122)	(76.3, 114)	(76.1, 120)	na	na	na
T_{max} (h)	Median	0.75	0.50	0.50	0.75	0.50	0.50
	Range	0.50-2.00	0.50-1.00	0.50-1.00	0.50-1.00	0.50-2.00	0.50-1.00
	J-W[b]	0.00	0.00	0.00	na	na	na
$t_{½}$ (h)	Arithmetic Mean	1.96	2.49	3.14	2.14	2.85	3.50
	Range	1.69-2.40	2.06-3.60	2.56-3.79	1.80-2.34	2.13-3.93	2.89-3.81
	J-W[b]	-0.19	-0.36	-0.36	na	na	na

Source: Tables 13.5.2.1 and 13.5.3
Abbreviation: CI = confidence interval; J = Japanese; na = not applicable; W = Westerner
[a] Ratio of Geometric Mean (Japanese / Westerners).
[b] Difference of Median or Arithmetic Mean (Japanese -Westerners).

(Source – Table 14, Study A3921036 report)

A separate study also characterized the single- and multiple-dose PK of tofacitinib in healthy Chinese subjects (Table 11). The PK characteristics of tofacitinib in Chinese subjects were similar to that observed in subjects from Western or Japanese ethnicities - a rapid absorption with T_{max} of approximately 0.5 hrs, short elimination half-life of about

Table 11: Summary of PK parameters in Chinese subjects

CP-690,550 Parameter (Units)	Summary Statistics[a] by Treatment: Day 1 (Single-Dose)	Day 6 (Multiple-Dose)
N	12	12
AUC_{inf} (ng.hr/mL)	274.8 (13)	NA
AUC_{last} (ng.hr/mL)	273.8 (13)	NA
AUC_{tau} (ng.hr/mL)	265.4 (13)	275.0 (12)
C_{max} (ng/mL)	98.28 (40)	89.19 (33)
T_{max} (hr)	0.500 (0.250-2.00)	0.500 (0.250-2.00)
C_{min} (ng/mL)	NA	2.265 (38)
C_{trough} (ng/mL)	NA	4.688 (38)
$t_{½}$ (hr)	3.319 (12)	2.479 (11)
R_{ac}	NA	1.036 (10)

Source: Table 14.4.3
N = number of subjects in the treatment group; NA = not applicable; CV = coefficient of variation.
Parameters are defined in Table 5.
[a] Geometric mean (%CV) for all except: median (range) for T_{max}; arithmetic mean (%CV) for $t_{½}$

(Source – Table 13, Study A3921065 report)

2.6.2.6 Renal Impairment

Renal function affected tofacitinib exposure as shown in Figure 11**Error! Reference source not found.** based on a single dose PK study, such that exposure increased with decline in renal function. Subjects with mild, moderate, and severe renal impairment had 41% (-5%, 109%), 71% (14%, 157%), and 156% (69%, 287%) respective increase in AUC compared to subjects with normal renal function (Table 12**Error! Reference source not found.**). Terminal half-life also increased with decrease in renal function; median value for normal renal function was 2.48 hrs, for mild renal impairment was 2.52 hrs, for moderate renal impairment was 2.68 hrs and for severe renal impairment was 3.77 hrs.

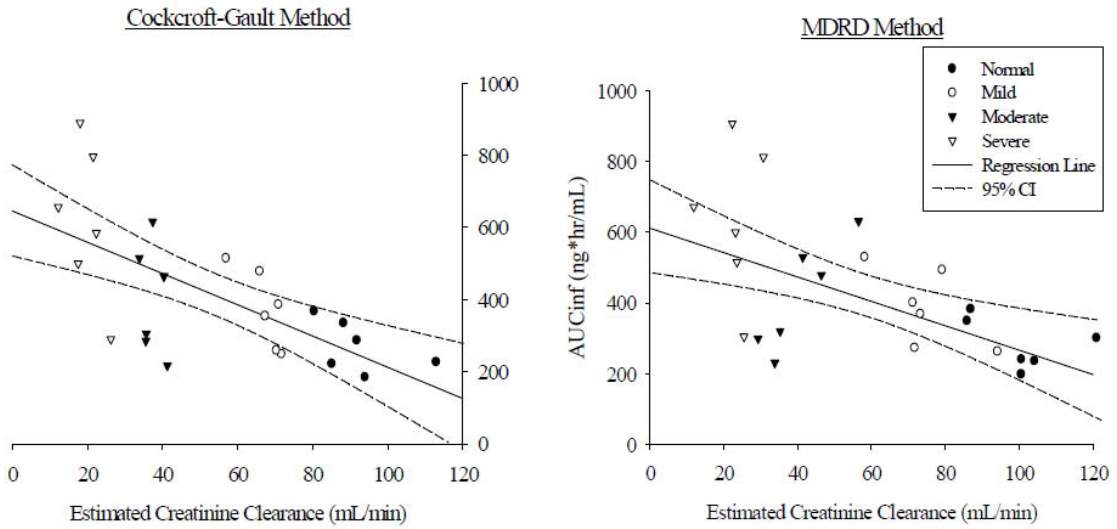


Figure 11: Individual $AUC_{0\text{-}inf}$ vs. calculated creatinine clearances following a single 10 mg

dose of CP-690,550 in subjects with normal renal function, and in subjects with mild, moderate, and severe renal impairment (Sponsor reported based on study A3921006, subjects group may change based on new renal guidance; see reviewer's comment below).

(Source – Figure C, Study A3921006 report)

Table 12: Geometric mean ratio and 90% CI for comparison of PK parameters between renally impaired subjects vs. normal renal function

	Test	Reference	GM Ratio [%Ref]	CI_90_lower	CI_90_Upper
AUC	Mild	Normal	140.92	94.81	209.48
	Moderate	Normal	171.43	114.45	256.78
	Severe	Normal	255.73	169.04	386.89
C_{max}	Mild	Normal	101.29	68.87	148.98
	Moderate	Normal	102.46	69.15	151.83
	Severe	Normal	120.65	80.64	180.53

A separate study was conducted in ESRD subjects maintained on hemodialysis. Comparison of PK in ESRD subjects from this study with that of PK for same formulation in healthy subjects from another study, showed 37% increase in AUC and 20% increase in Cmax. The reason for low relative increase in exposure compared to that seen in subjects with severe renal impairment is not known but for ESRD the estimation of change in exposure was based on cross study comparison. This study in ESRD subjects also demonstrated that of the amount cleared by renal pathway, about 73% was extracted during dialysis, suggesting that tofacitinib is highly dialyzable.

A 14-day multiple dose study in healthy subjects was also conducted to assess the impact of CP-690,550 on renal function. No significant effect on GFR (based on iohexol serum clearance), CLCr (based on 24 hr urine collection) or estimated renal plasma flow (based on para-aminohippuric acid clearance) was observed at least after 14 days treatment with CP-690,550, with or without adjusting for placebo effect (Table 13).

Table 13: Summary of results for iohexol serum clearance, CrCL and PAH renal clearance

	Ratios of Adjusted Geometric Means (90% CI)		
	Day15 / Day1 ratio for CP-690,550	Day15 / Day1 ratio for placebo	Ratio of Day15 / Day1 ratio for CP-690,550 to Day15 / Day1 ratio for placebo
Iohexol Serum Clearance	0.995 (0.942, 1.05)	0.911 (0.846, 0.982)	1.09 (0.997, 1.20)
CrCL	0.948 (0.893, 1.01)	0.905 (0.856, 0.956)	1.05 (0.967, 1.14)
PAH Renal Clearance	0.925 (0.819, 1.04)	0.946 (0.779, 1.15)	0.978 (0.783, 1.22)

CI = confidence interval, CrCL = creatinine clearance, PAH = para-aminohippuric acid

(Source – Table S3, Study A3921033 report)

Reviewer's comment

1. Note that the above reported percent change in tofacitinib pharmacokinetics based on varying renal function are calculated based on classification of patients as per new FDA renal guidance: creatinine clearance for Normal subjects - ≥90 mL/min, Mild renal impairment- 60-89 mL/min, Moderate renal impairment- 30-59 mL/min and severe renal impairment- 15-29 mL/min. Creatinine clearance cut-offs used by the sponsor for the respective groups were: >80 mL/min, >50 and ≤80 mL/min, ≥30 and ≤50 mL/min and <30 mL/min.

2. Observed mean plasma concentration – time profile data for subjects with moderate and severe renal impairment were modeled using WinNonlin version 5.2.1. The parameters obtained were then used to simulate plasma concentration – time profiles for different dosing regimens (Figure 12). These simulated concentration – time profiles for alternative dosing regimens were used to guide dosing recommendations by matching the exposure (AUC calculated by non-compartmental analysis) with that obtained for 5 mg tofacitinib dose in subjects with normal renal function.

   Calculated PK parameters for alternative dosing regimens are listed in Table 14. Based on exposure matching, the recommended dose for moderate and severe renal impairment subjects is:

   - if both 5 and 10 mg BID dose are approved, tofacitinib dose should not exceed 5 mg BID
   - if only 5 mg BID is approved, a reduced tofacitinib dose of 5 mg QD is recommended

For subjects with mild renal impairment, no dose adjustments are recommended.

Table 14: Steady-state PK parameters calculated based on simulated profiles

Population	Dose	Dosing Regimen	AUC_{48-72} ng/mL*hr	$T_{1/2}$ hr	C_{max} ng/mL
Normal	5 mg	BID	197	1.58	38.56
	10 mg	BID	394	1.58	77.13
Mild Renal Impairment	3 mg	BID	203	2.39	28.05
	5 mg	BID	338	2.39	46.75
	5 mg	QD	169	2.39	45.35
Moderate Renal Impairment	3 mg	BID	244	3.12	27.51
	5 mg	BID	407	3.12	45.85
	5 mg	QD	204	3.12	42.86
Severe Renal Impairment	2 mg	BID	249	4.08	23.24
	3 mg	BID	373	4.08	34.85
	5 mg	BID	621	4.08	58.09
	5 mg	QD	311	4.08	51.40

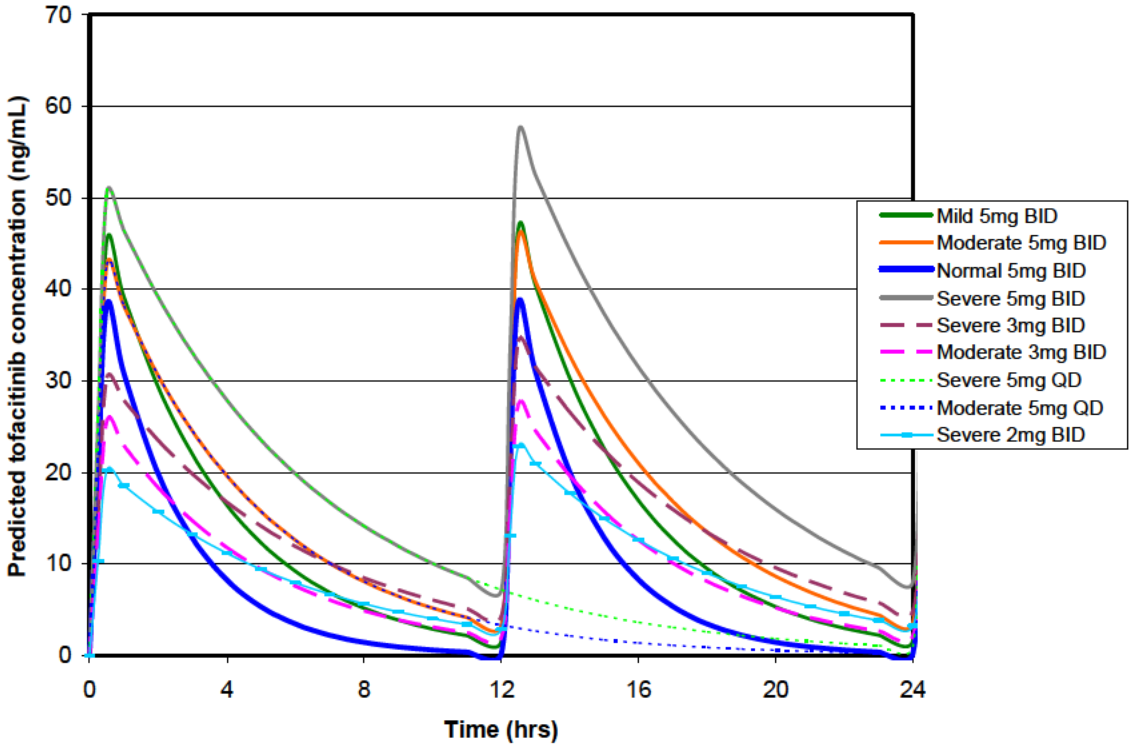


Figure 12: Simulated plasma concentration-time profiles for subjects with normal renal function and renal impairment

2.6.2.7 Hepatic Impairment

Mild hepatic impairment (Child Pugh A) did not alter tofacitinib exposure compared to subjects with normal hepatic function. Mean change in AUC and C_{max} was approximately 3%; however, 90% CI on difference was wider and ranged from -25% to 36%. No dose adjustments are recommended for mild hepatic impairment (Table 15).

In subjects with moderate hepatic impairment (Child Pugh B), there was a 65% increase in CP-690,550 $AUC_{(0-\infty)}$ (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 (Table 15).

Tofacitinib was not evaluated in patients with severe hepatic impairment because of the risk of immunosuppressing patients who are already at risk of infection from their hepatic disease. Therefore; tofacitinib is not recommended in patients with severe hepatic impairment

Reviewer's comment
Method similar to that described for dosing adjustment in subjects with renal impairment was used to identify the dosing adjustments for subjects with hepatic impairment. Based on 64% increase in exposure for moderate hepatic impairment following dose adjustments are recommended for subjects with moderate hepatic impairment based on exposure matching (Figure 13 and Table 16):

- if both 5 and 10 mg BID dose are approved, tofacitinib dose should not exceed 5 mg BID
- if only 5 mg BID is approved, a reduced tofacitinib dose of 5 mg QD is recommended

Table 15: Summary of Statistical Comparisons of PK Parameters: Mild and Moderate Hepatic impairment groups vs. normal hepatic function group

Parameter, units	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Test	Reference		
Mild hepatic impairment (test) vs normal hepatic function (reference)				
AUC_{inf}, ng.hr/mL	366.0	354.8	103.15	78.31, 135.85
AUC_{last}, ng/mL	364.3	353.5	103.06	78.21, 135.81
C_{max}, ng/mL	60.08	60.45	99.39	75.01, 131.70
Moderate hepatic impairment (test) vs normal hepatic function (reference)				
AUC_{inf}, ng.hr/mL	583.9	354.8	164.57	124.95, 216.75
AUC_{last}, ng/mL	581.1	353.5	164.38	124.74, 216.62
C_{max}, ng/mL	89.92	60.45	148.75	112.26, 197.11

Source: Table 13.5.3.1
Abbreviations: AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), CI = confidence interval, C_{max} = maximum observed concentration
[a] The ratios (and 90% CIs) are expressed as percentages.

(Source – Table S4, Study A3921015 report)

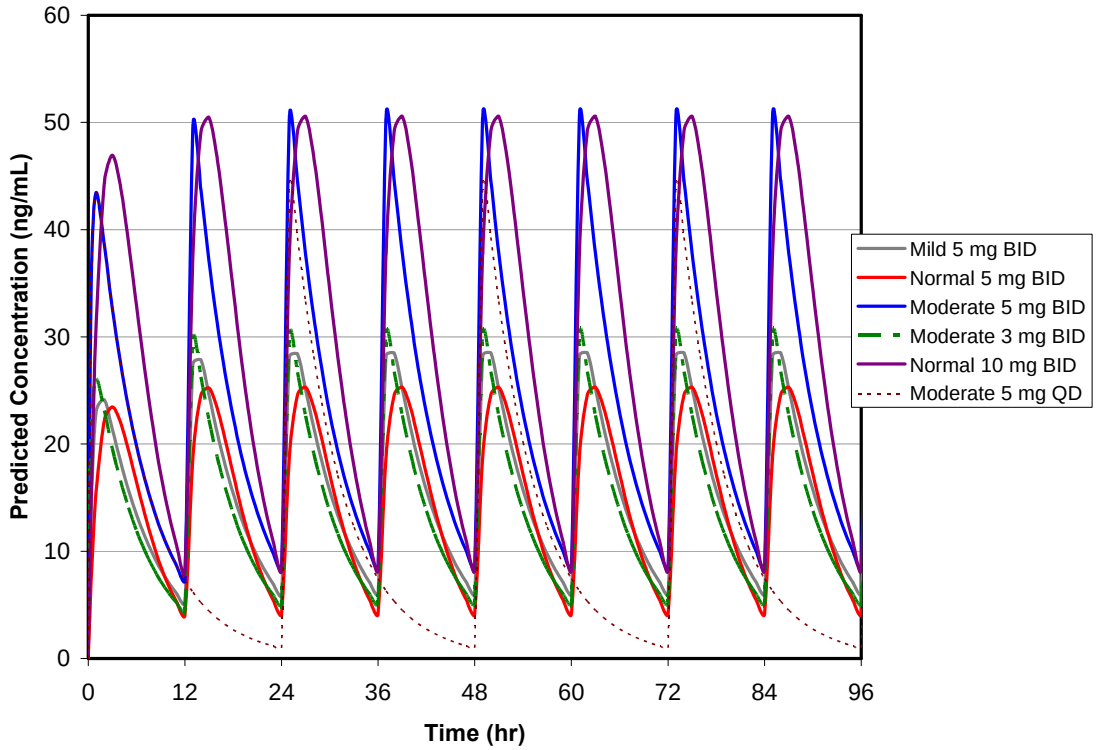


Figure 13: Simulated plasma concentration-time profiles for subjects with normal hepatic function and hepatic impairment

Table 16: Steady-state PK parameters calculated based on simulated profiles for subjects with normal hepatic function or hepatic impairment

Population	Dose	Dosing Regimen	AUC_{48-72}	$T_{1/2}$	C_{max}
Normal	5 mg	BID	362	2.66	25.29
	10 mg	BID	723	2.66	50.58
Mild Hepatic Impairment	5 mg	BID	387	4.36	28.52
Moderate Hepatic Impairment	5 mg	BID	590	4.16	50.61
	3 mg	BID	354	4.16	30.37
	5 mg	QD	295	4.16	44.33

2.6.3 Does genetic variation impact exposure and/or response?

The in-vitro and mass-balance suggest that tofacitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C19.

The sponsor recommends dose adjustment for patients receiving drug(s) that inhibit both CYP3A4 and CYP2C19 (e.g., fluconazole) because of an approximate two-fold increase in exposure. However, tofacitinib dose adjustment is not warranted when coadministered with a CYP2C19 inhibitor.

The pharmacogenetic analysis conducted by the sponsor suggests that CYP2C19 metabolic status has little effect on tofacitinib PK. Therefore, dosing recommendations based on genotype alone do not appear to be indicated. Please see Genomics review by Dr. Jeffrey Kraft for assessment of the impact of genetic variation on tofacitinib exposure.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

The potential for drug-drug interaction because of induction or inhibition of CYP enzymes by tofacitinib is less likely at therapeutic concentrations. Please see sections 2.7.2 and 2.7.4 for further details.

2.7.2 Is the drug a substrate of CYP enzymes?

Yes, metabolism is a major pathway of clearance for tofacitinib. In vitro studies using human recombinant CYP450 isoforms indicated that CP-690,550 is primarily metabolized by CYP3A4 and CYP2C19 with minimal metabolism from CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2D6, CYP2E1, and CYP3A5. In vitro and in vivo studies with ketoconazole showed that CYP3A4 was primarily responsible for metabolism of tofacitinib.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

In vitro studies demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A activities. IC_{50} values could not be calculated since tofacitinib did not inhibit any enzyme activity more than 27% for the tested concentrations of up to 30 μM. Given a steady state unbound C_{max} of approximately ~310 nM[2] or 0.31 μM for a dose of 10 mg BID, the C_{max}/IC_{50} ratios are <0.01, suggest a low potential for tofacitinib to influence the metabolism of coadministered drugs that are metabolized by CYP450 enzymes (Table 17).

At clinically relevant concentrations (i.e., steady-state concentrations for 10 mg bid=~310 nM or 0.31 μM[2]), no induction of CYP3A4 and CYP1A2 enzymes was seen in in vitro studies.

Table 17: IC50 values for inhibition of metabolic enzymes and transporters by tofacitinib

CYPs/Transporters	IC50 μM	[I] / IC50	[I2] / IC50
CYP1A2, 2B6, 2C8, 2C9, 2C19,2D6	>30	~0.01	4.27
P-gp	311	0.000990	0.41
OCT	150	0.002053	0.85
OATP1B1	55.3	0.005569	2.31
OATP1B3	ND		

ND – Not determined because for OATP1B3 no inhibition was observed up to tested concentration of 100 μM
[I] = maximum total inhibitor concentration in plasma = Cmax value for the to-be-marketed formulation from the pivotal bioequivalence study (96.4 ng/mL=0.31μM)
[I2] = For inhibitors which are dosed orally it is equal to (Molar Dose/250 mL) (For tofacitinib [I2] is equal to 128 μM)

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

In vitro permeability assessments indicated that tofacitinib is a substrate for P-gp, but not a substrate of BCRP.

Tofacitinib has low potential to inhibit P-gp with an estimated IC_{50} value of 311 μM. At a steady-state unbound C_{max} of ~ 310 nM and projected gut concentration of ~128 μM using a gut dilution factor of 250 mL) following a 10 mg BID dose, the systemic [I]/IC50 ratio is ~0.001 and the gut [I]/IC50 ratio is ~0.4 (Table 17). Both of these ratios are significantly below the level where a digoxin interaction study would be warranted, i.e., >0.1 and >10, respectively.

Tofacitinib also has low potential to inhibit hOCT2 and OATP1B1 at clinically relevant concentrations based on in vitro assessment in hOCT2-transfected human embryonic kidney (HEK)-293 cells. Systemic [I]/IC50 and [I2]/IC50 were below the threshold at which further in vivo evaluation would be warranted (Table 17). Tofacitinib was not an inhibitor of OATP1B3.

[2] C_{max} of approximately ~310 nM or 0.31 μM is equal to the Cmax of the to-be-marketed formulation (i.e., 96.2 ng/mL), which is taken from bioequivalence study bridging the commercial formulation with the clinical formulation (section 2.8.2). Note that tofacitinib PK after single-dose and multiple-dose are similar

2.7.5 Are there other metabolic/transporter pathways that may be important?

No other metabolic enzyme or transported pathway is known to be important for disposition of tofacitinib in addition to those already discussed in sections 2.7.2 and 2.7.4

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?

Among extrinsic factors only the effect of coadministration with other drugs on tofacitinib exposure has been evaluated, which is discussed under section 2.7.7. Other extrinsic factors such as effect of comorbidities on drug exposure have not been evaluated.

2.7.7 What are the drug-drug interactions?

Drug interaction was evaluated as follows and the results are summarized in Table 18 and Table 21:

- Effect of tofacitinib on PK of coadministered drugs
- Effect of coadministered drugs on tofacitinib PK

Table 18: Effect of tofacitinib on coadministered drugs

Tofacitinib Regimen	Substrate	GMR (90% CI)	
		AUC	C_{max}
Tofacitinib 30 mg BID (coadministered with Microgynon® on days 10-11)	**Microgynon®** (30 µg ethinylestradiol (EE) + 150 µg levonorgestrel (LNG)) (test arm: coadministration with tofacitinib on day 10; reference arm: monotherapy on day 1)		
	EE	106.55 (98.9-114.8)	89.6 (82-98)
	LNG	100.9 (94.7-107.4)	112.2 (105.3-119.5)
Tofacitinib 30 mg BID (coadministered with midazolam on days 6-7)	**Midazolam**† (CYP3A4 substrate) (test arm: coadministration with tofacitinib on day 7; reference arm: monotherapy 2 mg oral syrup on day 1)	104 (95.6-113.1)	102.2 (96-108.9)
Tofacitinib 30 mg BID (monotherapy on days 3-6 and coadministered with methotrexate on day 7)	**Methotrexate** (test arm: coadministration with tofacitinib on day 7 ; reference arm: monotherapy on day 1)	89.5 (77.4-103.6)	87.3 (76-100.1)

Reviewer's comments

1. No dose adjustments are recommended for oral contraceptive (Microgynon), midazolam and methotrexate when coadministered with tofacitinib

Table 19: 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)
Rifampin† (potent P-gp and CYP3A4 inducer) 600 mg QD (monotherapy on days 1 to 7)	Tofacitinib 30 mg QD (test arm: on day 8 following 7 days of rifampin administration; reference arm: single-dose on day 1)	16.1 (14.2-18.2)	26.3 (22.6-30.6)
Methotrexate –individualized single-dose (15-25 mg/week)	Tofacitinib 30 mg BID (test arm: coadministration with methotrexate on day 7; reference arm: monotherapy on days 3-6)	103.1 (99-107.3)	102.7 (93.8-112.5)
Tacrolimus –5 mg BID or adjusted dose to achieve pre-set concentration on days 1 to 7 as monotheapy and on day 8 with tofacitinib.	Tofacitinib 10 mg (test arm - coadministration with tacrolimus on day 8; reference arm: monotherapy on day 1)	121.1 (113.2-129.6)	90.8 (83.6-99)
Cyclosporine –200 mg BID or adjusted dose to achieve pre-set concentration on days 1 to 5 as monotheapy and on day 6 with tofacitinib.	Tofacitinib 10 mg (test arm - coadministration with cyclosporine on day 6; reference arm: monotherapy on day 1)	173.1 (161.8-185.3)	83.2 (71.4-97)

Reviewer's comments

1. No significant change in exposure of tofacitinib was observed following coadministration with methotrexate; therefore, no dose adjustments are recommended.
2. Following coadministration with tacrolimus, tofacitinib AUC increased by ~21% and C_{max} reduced by ~10%. However, both tofacitinib and tacrolimus are immunosuppresants and have not been studied together. Therefore, because of potential for pharmacodynamic drug-drug interaction coadministration of tofacitinib with tacrolimus is not recommended.
3. Following coadministration with cyclosporine, tofacitinib AUC increased by ~73% and C_{max} reduced by ~17%. However, both tofacitinib and cyclosporine are immunosuppresants and have not been studied together. Therefore, because of

potential for pharmacodynamic drug-drug interaction coadministration of tofacitinib with cyclosporine is not recommended.

4. Coadministration with rifampin significantly reduced AUC and C_{max} of tofacitinib by ~84% and 74%, respectively. These lower exposures will result in inefficacious concentrations; therefore, coadministration with rifampin or other strong CYP3A inducers is not recommended.
5. A significant increase in tofacitinib exposure was observed following coadministration with ketoconazole and fluconazole. The steps taken to identify a suitable dosing regimen for these cases are outline below:
    i. Observed mean plasma concentration – time profile data from DDI studies for ketoconazole and fluconazole were modeled using WinNonlin version 5.2.1. The parameters obtained were then used to simulate plasma concentration – time profiles for different dosing regimens (Figure 14 and Figure 15, respectively for ketoconazole and fluconazole).
    ii. These 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 exposures (AUCs) to that obtained after administration of 5 mg BID (if only 5 mg BID dose is approved) or 10 mg BID (if both 5 mg BID and 10 mg BID doses are approved) tofacitinib as single therapy.
    iii. To confirm that simulated profiles were representative of the observed data, AUC and C_{max} values from simulated concentration-time profiles were compared with the mean values reported in the sponsor reports. These values were comparable for both scenarios- ketoconazole and fluconazole.
6. Based on steps outlined in point 4, tofacitinib dosing recommendations for coadministration with ketoconazole and fluconazole is:
    a. if both 5 and 10 mg BID dose are approved, tofacitinib dose should not exceed 5 mg BID
    b. if only 5 mg BID is approved, a reduced tofacitinib dose of 5 mg QD is recommended
7. The plasma concentration-time profiles for 5 mg QD and other dosing regimens are shown in Figure 14 and Figure 15. Calculated PK parameters based on these simulated plasma concentration – time profiles are listed in Table 20 and Table 21.

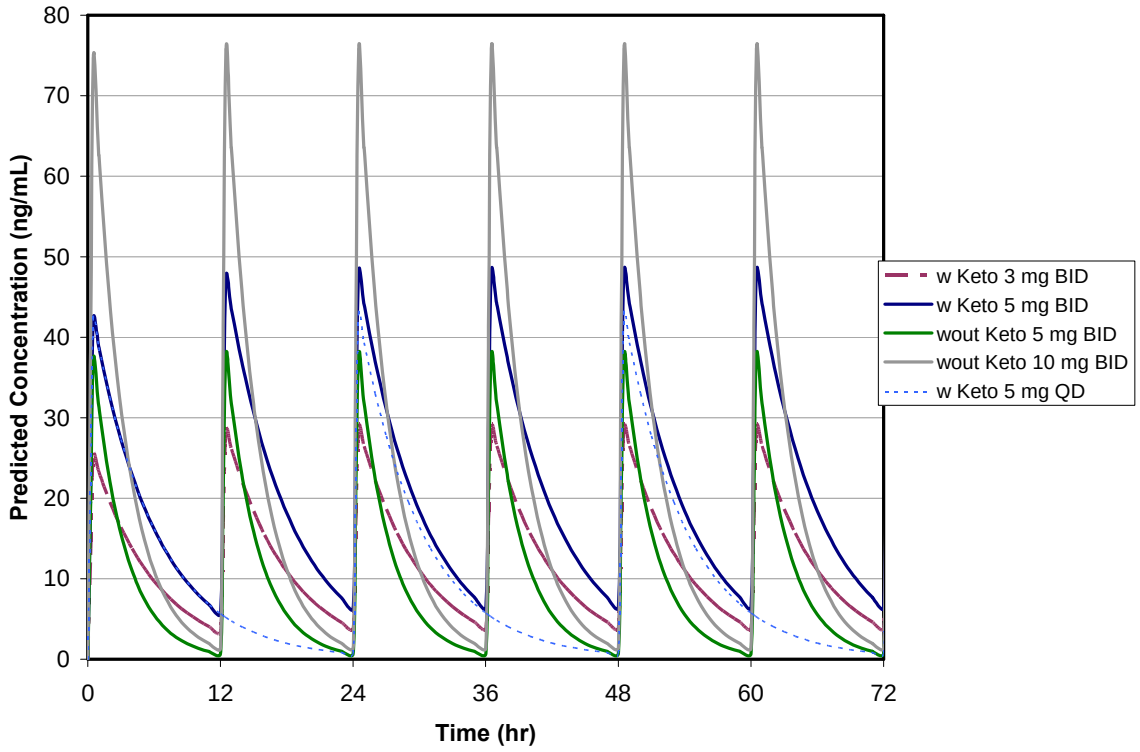


Figure 14: Simulated plasma concentration - time profiles for tofacitinib 3/5/10 mg BID administered with or without ketoconazole
(w: with, wout: without, keto: ketoconazole)

Table 20: Steady-state PK parameters calculated based on simulated profiles with and without ketoconazole

Population	Dose	Dosing Regimen	AUC_{48-72} ng/mL*hr	$T_{1/2}$ hr	C_{max} ng/mL
Without ketoconazole	5 mg	BID	235	1.99	37.83
	10 mg	BID	470	1.99	75.67
With ketoconazole	5 mg	BID	506	3.96	48.19
	10 mg	BID	1012	3.96	96.38
	3 mg	BID	304	3.96	28.91
	5 mg	QD	253	3.96	42.93

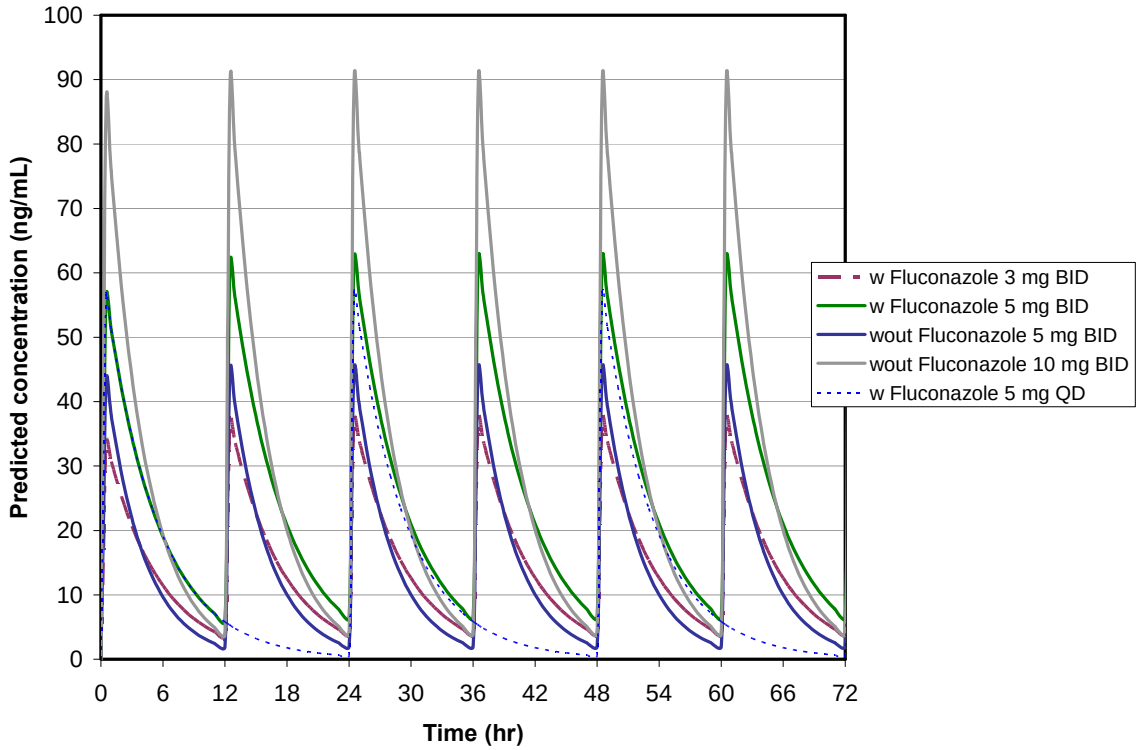


Figure 15: Simulated plasma concentration - time profiles for tofacitinib 3/5/10 mg BID administered with or without fluconazole
(w: with, wout: without)

Table 21: Steady-state PK parameters calculated based on simulated profiles with and without fluconazole

Population	Dose	Dosing Regimen	AUC_{48-72} ng/mL*hr	$T_{1/2}$ hr	C_{max} ng/mL
Without fluconazole	5 mg	BID	341	2.54	45.10
	10 mg	BID	683	2.54	90.20
With fluconazole	5 mg	BID	601	3.51	62.26
	10 mg	BID	1203	3.51	124.52
	3 mg	BID	361	3.51	37.36
	5 mg	QD	301	3.51	56.95

2.7.8 Does the label specify coadministration of another drug?

No, the tofacitinib label does not mention specific coadministration with other drugs.

2.7.9 What other co-medications are likely to be administered to the target population?

All rheumatoid arthritis patients are likely to take tofacitinib in background of methotrexate. Tofacitinib is not recommended to be administered in background of other

biologics disease modifying anti-rheumatic drugs (DMARDs), but it has a potential to be administered with other anti-rheumatic drugs as listed in section 2.2.4 (excluding biologic DMARDs).

Rheumatoid arthritis is more likely to occur in old age patients; therefore, there is a potential for other drugs such as anti-hypertensives, anti-diabetic, anti-hyperlipidemic etc. to be administered with tofacitinib.

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

Potential for pharmacodynamic drug-drug interactions with tacrolimus and cyclosporine is discussed under 2.7.7. Theoretically there is also a possibility that other immunosuppressive drugs which act by JAK kinase or other pathways, if coadministered, may affect the safety profile of tofacitinib.

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Tofacitinib can be considered a BCS class 3 drug because of high aqueous solubility and moderate permeability.

The aqueous pH solubility of tofacitinib (the citrate salt) was determined to be >0.04 mg/mL, which is the concentration obtained from dissolving the highest dose strength of 10 mg tablet in 250 mL solution. Thus the CP-690,550-10 solubility profile meets the high solubility criteria set forth based on the BCS principles.

The human oral bioavailability study showed that the mean absolute oral bioavailability of the commercial tofacitinib tablet was 74%, which is less than the 90% criterion described in the BCS guidance for a Class I agent. In the human mass balance study, the mean total percentage of administered radioactive dose recovered was 94%, with 80% in the urine and 13.8% in the feces, which did not conclusively show that the fraction of dose absorbed was greater than 90%. In vitro permeability assessments also showed that apparent permeability (Papp) values of tofacitinib at concentrations 1x, 0.1x, and 0.001x of clinical dose (10 mg in 250 mL) were lower than that of metoprolol, which is a highly permeable compound and was used as the reference. Based on available data, tofacitinib appears to have low permeability based on BCS principles.

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

Clinical service formulation and commercial formulations had differences in excipients as shown in
Table 22. To bridge these formulations sponsor conducted a bioequivalence study comparing Phase 2B, Phase 3 and commercial formulation in a 3-way cross-over study.

All three formulations were bioequivalent to each other with geometric mean ratio and 90% CI for AUC and C_{max} parameters within 80-125% (
Table 23). The Division of Bioequivalence and GLP Compliance (DBGC) conducted an audit of the clinical and analytical portions of this bioequivalence study and found them acceptable. See review by Dr. Young Choi dated May 30, 2012.

Table 22: Comparison of composition of clinical trial and commercial tablet formulations of tofacitinib

Formulation Description	Phase 2A		Phase 2B		Phase 3	Commercial	
Strength	5 mg	20 mg	5 mg	1 mg	5 mg	5 mg	10 mg
Formulation ID	G02721AA	G02722AA	D0602459	D0602458	D0804138	D0904981	D0904982
Composition (mg)							
CP-690,550 Citrate[1]	(b) (4)						
Microcrystalline Cellulose							
Lactose anhydrous (b) (4)							
Croscarmellose Sodium							
Magnesium Stearate (b) (4) (b) (4)							
(b) (4)							
Total Tablet Weight (mg)	(b) (4)					206.000	(b) (4)

(b) (4)

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

Table 23: Statistical summary of treatment comparisons for plasma CP-690,550 parameters following single 10 mg oral tablet doses

Parameter (Units)	Adjusted Geometric Means: Test	Adjusted Geometric Means: Reference	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
1 x 10 mg Commercial Image tablet (test) versus 2 x 5 mg Phase 3 tablets (reference)				
AUC_{inf} (ng.hr/mL)	277.0	278.3	99.54	96.69, 102.47
AUC_{last} (ng.hr/mL)	275.5	276.8	99.52	96.68, 102.45
C_{max} (ng/mL)	96.46	91.69	105.20	95.57, 115.80
1 x 10 mg Commercial Image tablet (test) versus 2 x 5 mg Phase 2B tablets (reference)				
AUC_{inf} (ng.hr/mL)	277.0	279.9	98.97	96.13, 101.88
AUC_{last} (ng.hr/mL)	275.5	278.3	98.98	96.15, 101.89
C_{max} (ng/mL)	96.46	102.7	93.88	85.31, 103.32
2 x 5 mg Phase 3 tablets (test) versus 2 x 5 mg Phase 2B tablets (reference)				
AUC_{inf} (ng.hr/mL)	278.3	279.9	99.43	96.62, 102.31
AUC_{last} (ng.hr/mL)	276.8	278.3	99.45	96.65, 102.34
C_{max} (ng/mL)	91.69	102.7	89.24	81.20, 98.08

Source: Table 14.4.4.1
Parameters are defined in Table 4.
CI = confidence interval.
[a] The ratios (and 90% CIs) are expressed as percentages.

(Source – Table 14, Study A3921075 report)

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 tofacitinib was assessed at two dose levels for 10 mg commercial tablet (in study A3921076) and 50 mg Phase 2A tablet (in study A3921005). Coadministration of tofacitinib with meal had no impact on AUC (point estimate and 90% CI were contained within 80-125% for both studies) but mean C_{max} deceased by 32% and 26%. Tofacitinib average exposure was a better predictor of efficacy than C_{max} (see pharmacometrics review, section 1.1.2, Figure 17); therefore, no dose adjustments are recommended based on 26-32% decrease in C_{max} and tofacitinib can be administered without regard to meals.

Table 24: Comparison of Food Effect Data Following 10 mg commercial tablet and 50 mg Phase 2A tablet (studies A3921005 and A3921076)

PK Parameters	Adjusted Geometric Mean: Test (Fed)	Adjusted Geometric Mean: Reference (Fasted)	Statistical Comparison: Ratio (Test/Ref. %)	Statistical Comparison: 90 % CI (%)
A3921076: commercial tablet (1 x 10 mg)	N=16	N=16		
AUC(0-∞) (ng·h/mL)	285.7	269.5	106.03	102.62, 109.56
Cmax (ng/mL)	63.10	92.55	68.18	58.39, 79.61
A3921005: Phase 2A tablet (2 x 20 mg and 2 x 5 mg)	N=12	N=12		
AUC(0-∞) (ng·h/mL)	1579.30	1373.84	114.96	110.20, 119.91
Cmax (ng/mL)	264.38	356.07	74.25	67.97, 81.11

(Source – Table 21, 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, bioequivalence was only tested for the 10 mg dose level of the to-be-marketed formulation and not for the 5 mg dose level. Bioequivalence was tested for 10 mg strength of the commercial formulation. Sponsor stated that the lower strength of 5 mg commercial tablet (b) (4) shares the same manufacturing process. Please refer to review by Office of New Drug Quality Assessment (ONDQA) reviewer for further details on compositional proportionality of the 5 mg dose strength of the commercial tablet.

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?

Analytical methods used to measure the parent drug in different studies are listed in Table 25. Two of the methods, which were used in most of the studies for analysis of tofacitinib in heparinized plasma, are summarized below.

Analytical method report # A3929008

Tofacitinib was extracted from human sodium heparinized plasma by 96-well solid phase extraction (Phenomenex Strata-XC 10mg plate). Before the extraction, radiolabeled tofacitinib (i.e., [^{13}C,^{15}N] CP-690,550) was added as an internal standard. The samples were eluted with 13% ammonium hydroxide (NH_4OH) 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 Phenomenex Synergi Polar RP 4μ column with a mobile phase of 40% 10mM ammonium acetate and 60% methanol (with 0.05% formic acid). The lower limit of quantitation (LLOQ) for tofacitinib in human plasma was 1 ng/mL, with linearity demonstrable to 100 ng/mL, using a sample volume of 300 μL.

Analytical method report # A3929011

The bioanalytical methods to measure tofacitinib in human plasma PK samples were developed and validated at (b) (4) Tofacitinib was extracted from sodium heparinized human plasma by 96-well solid phase extraction. Before the extraction, radiolabeled tofacitinib (i.e., [^{13}C,^{15}N] CP-690,550) was added as an internal standard. The samples were eluted with 13% NH_4OH 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 40% 10 mM ammonium acetate and 60% methanol (with 0.05% formic acid). The lower limit of quantitation (LLOQ) for CP-690,550 in human plasma was 0.100 ng/mL, with linearity demonstrable to 350 ng/mL, using a sample volume of 300 μL.

Table 25: Summary of analytical methods for analysis of tofacitinib in clinical

Pfizer Method Validation Report No.	Matrix	Assay laboratory	Sensitivity (ng/mL)	Inter-assay Precision	Inter-assay Accuracy	Linearity (ng/mL)	Protocol No. (CTD No.)
A3929001	Serum	Pfizer PDM - Groton	1.00	≤4.5%	98.5% to 102.3%	1.00 to 100	A3921002
A3929002	Urine	Pfizer PDM - Groton	1.00	≤3.6%	98.5% to 101.3%	1.00 to 100	A3921002
A3929003	Serum	(b) (4)	1.00	≤2.4%	98.0% to 98.3%	1.00 to 100	A3921003
A3929004	Urine		1.00	≤3.2%	99.1% to 102.1%	1.00 to 100	A3921003 A3921006 A3921013 A3921036
A3929005	Renal Dialysate		1.00	≤3.3%	99.1% to 100.6%	1.00 to 100	A3921004
A3929006	EDTA Plasma		1.00	≤5.1%	103.2% to 104.9%	1.00 to 100	A3921004
A3929007	Ultrafiltrate		1.00	≤3.5%	97.8% to 101.1%	1.00 to 100	A3921004
A3929008	Heparin Plasma		1.00	≤3.2%	105.0% to 107.5%	1.00 to 100	A3921004 A3921005 A3921006 A3921010 A3921013 A3921014 A3921019 A3921033
A3929011	Heparin Plasma		0.100	≤8.3%	101.4% to 106.3%	0.100 to 350	A3921015 A3921020 A3921025 A3921028 A3921035 A3921036 A3921039 A3921040 A3921054 A3921056 A3921064 A3921065 A3921071 A3921075 A3921076 A3921077

(Source – Table A1.2, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

2.9.2 Which metabolites have been selected for analysis and why?

No metabolites were measured in PK samples. As stated in section 2.5.7 (Table 7), 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?

Table 25 presents a summary of analytical methods used for quantification of tofacitinib and lists out the respective validation report numbers. 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 A3923011 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.

For the analytical method A3929008, standard curve range was from 1 to 100 ng/mL. The calibration curves were obtained by using a 1/concentration^2 weighting factor in a linear regression model of peak area ratio vs. concentration.

2.9.5.1 What are the lower and upper limits of quantitation?

LLOQ and ULOQ for A3929008 analytical method were 1 ng/mL and 100 ng/mL, respectively. Ten fold dilution factor was also validated for concentrations above 100 ng/mL.

LLOQ and ULOQ for A3929011 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 methods A3929008 and A3929011 are listed in Table 26 and

Table 27, respectively. For both analytical methods bias and imprecision for 10 fold dilution factor was less 6%.

Table 26: Accuracy and Precision of Tofacitinib Analytical LC/MS/MS Assay (Validation Report # A3929008)

QC Sample Concentrations (ng/mL)	Accuracy (%)		Precision (%)	
	Range of Intra-Assay Daily Mean	Inter-Assay Mean	Range of Intra-Assay Daily Mean	Inter-Assay Mean
3.00	104.7-109.7	107.5	2.3-3.1	3.20
20.0	101.5-105.5	105.0	1.0-1.7	1.00
80.0	105.0-106.9	105.4	1.3-1.4	2.00

Source: Validation Report A3929008

(Source – Table 6, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

Table 27: Accuracy and Precision of Tofacitinib Analytical LC/MS/MS Assay (Validation Report # A3929011)

QC Sample Concentrations (ng/mL)	Accuracy (%)		Precision (%)	
	Range of Intra-Assay Daily Mean	Inter-Assay Mean	Range of Intra-Assay Daily Mean	Inter-Assay Mean
0.100	95.1-109	103	5.8-6.5	8.3
0.300	95.0-110	104.3	3.4-6.8	7.1
4.00	98.2-110.8	106.3	1.6-2.9	4.9
40.0	99.2-107.5	103.5	0.6-2.6	3.4
280	97.5-107.5	101.4	1.0-6.2	5.3

Source: Validation Report A3929011

(Source – Table 6, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

The selectivity of both the methods 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.

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

For both the bioanalytical methods stability was demonstrated under different conditions as discussed below:

A3929008

Stability of tofacitinib was established under various conditions: stability of tofacitinib for at least 28 days at -20°C; three freeze thaw cycles at -20°C; stability of processed samples (auto sampler reinjection and reproducibility) for 26 hours, stability under ambient conditions (bench-top) for 48 hours. For each of these stability assessments %CV was less than 11%. Stock solution stability was also assessed for 75 days at 2-8°C.

A3929011

Stability of tofacitinib was established under various conditions: stability of tofacitinib for 693 days at -20°C; 391 days at -80°C; four freeze thaw cycles at -20°C and -80°C; stability of processed samples (auto sampler reinjection and reproducibility) for 75 hours at ambient temperature, stability under ambient conditions (bench-top) for 25 hours as well as stability of analyte primary stock (in 50% Acetonitrile stored at 2-8°C for 362 days) and working solution for analyte, tofacitinib (in 50:50 Acetonitrile:water) stored at 2-8°C for 20 days) and internal standard, radiolabeled tofacitinib or [^{13}C,^{15}N]CP-690,550 (2-8°C for 43 days). For each of these stability assessments deviation ranged between ≤15%.

2.9 Detailed Labeling Recommendations

At this point in time additional safety analysis is ongoing and selection of the final dosing regimen is pending. As such, detailed labeling comments are not incoporated in this review. Following are the global labeling comments for the sponsor based on available information at this time.

- Please revise the figure representing the results from DDI studies, food effect, and effect of intrinsic and extrinsic factors, such that results related to one particular aspect are close to each other (b) (4)

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

1. SUMMARY OF FINDINGS

1.1. Key Review Questions

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

1.1.1. Are the proposed labeling statements based on population pharmacokinetic analysis acceptable?

Yes, the following labeling statements, derived based on population pharmacokinetic analysis, are acceptable. For technical details, please refer to **RESULTS OF SPONSOR'S ANALYSIS** section of the review.

(b) (4)

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

Effectiveness of tofacitinib across multiple dose levels was evaluated in five Phase 2 studies – A3921019, A3921025, A3921035, A3921039, and A3921040. Of these two studies 1039 and 1040 were conducted in Japanese patients and were of 12 week duration. Study 1019 was of 6 week duration. Studies 1025 and 1035 were each of 24-week duration with primary efficacy endpoint measured at week 12 followed by 12 week of durability assessment. Dose-response results from global studies 1025 and 1035 which were of relatively longer duration are discussed below.

Study 1035

This study evaluated tofacitinib as monotherapy with an active comparator arm for adalimumab. The dose-response for ACR20, ACR50, ACR70, and DAS28-3(CRP) response rates based on observed data at week 12 is shown in Figure 16.

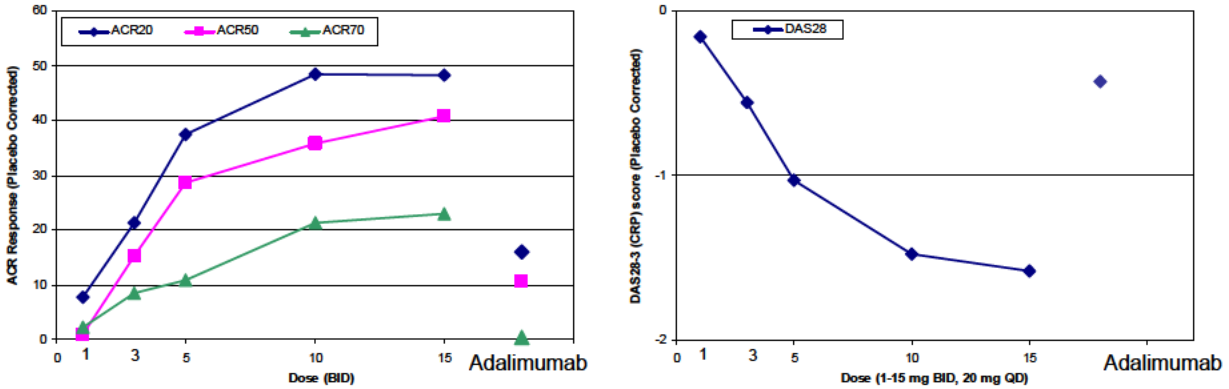


Figure 16: Placebo adjusted change from baseline in ACR 20 ACR 50, ACR 70 at week 12 for study A3921035

Study 1025

This study evaluated tofacitinib in the background of methotrexate treatment. The dose-response for ACR20, ACR50, ACR70, and DAS28-3(CRP) response rates based on observed data at week 12 is shown in Figure 17.

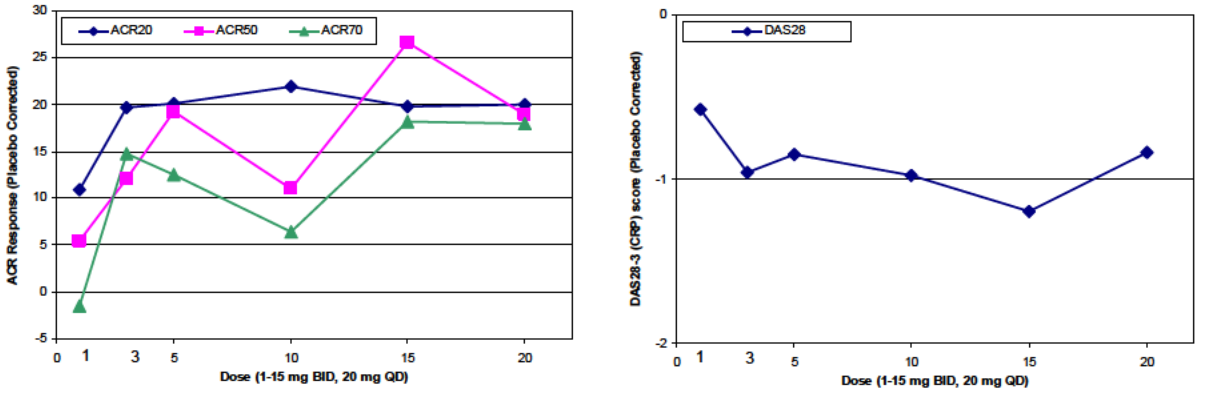


Figure 17: Placebo adjusted change from baseline in ACR 20 ACR 50, ACR 70 at week 12 for study A3921025

As shown in Figure 16, there was a trend of increase in ACR 20, ACR 50, ACR 70 and DAS 28 response at week 12 with increase in tofacitinib dose from 1 to 10 mg BID with relatively minor change between 10 and 15 mg BID dose when used as monotherapy. Also note that response for tofacitinib 3 mg BID and higher doses was comparable or better than the active comparator adalimumab. Note that the adalimumab response reported in Figure 16 was lower than that previously reported, that is because adalimumab was tested as single agent (not in background of methotrexate) in this study. Evaluation of longitudinal data showed that all tested dose levels except 1 mg BID were statistically better than placebo across treatment duration.

In study 1025, in background of methotrexate, dose related changes were seen from 1 mg onwards with no additional benefit beyond 3 mg. The dose response was almost flat across the range of doses from 3 mg BID to 15 mg BID and 20 mg QD for ACR 20 and DAS 28 endpoints (Figure 17). The dose response for ACR 50 and ACR 70 was not

consistent in this study. In this study, 20 mg QD dose had response similar to that observed for the same total daily dose given as 10 mg BID. The comparable efficacy for 20 mg QD and 10 mg BID suggest that $C_{average}$, and not the C_{max} and C_{trough}, may be a better predictor of efficacy. Longitudinal data from this study also showed that all doses except 1 mg BID were statistically better from placebo across treatment duration.

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

The dose response for safety was assessed based on phase 2 clinical studies 1025 and 1035. In addition, in all 5 phase 3 clinical trials both 5 and 10 mg dose of tofacitinib was evaluated for at least six months to one year duration, which provided important information about dose related safety.

Safety, as measured by laboratory parameters, such as LDL, HDL, serum creatinine, and absolute neutrophil counts are dose dependent. A trend of decrease in neutrophil counts and increase in LDLC, HDLC, total cholesterol and serum creatinine was observed with increase in dose in monotherapy study 1035 (Figure 18). There was a trend of increase in hemoglobin with increase in dose up to 5 mg BID followed by a decline was observed (sponsor described this relationship as an inverted U shape relationship). Trend for infections endpoint was not consistent in this study. In this study safety profile of monotherapy adalimumab appears to be comparable or better than the lower 3 mg BID dose of tofacitinib monotherapy; however, note that in clinical practice these drugs are more likely to be used in background of methotrexate or other drugs.

A similar trend of dose response was also observed in methotrexate background study1025 (Figure 19). In this study decline in hemoglobin followed the same U-shape trend as seen in study A3921035. Note that in this study 20 mg QD dose appears to have safety profile which is comparable to that observed for the same total daily dose given as 10 mg BID.

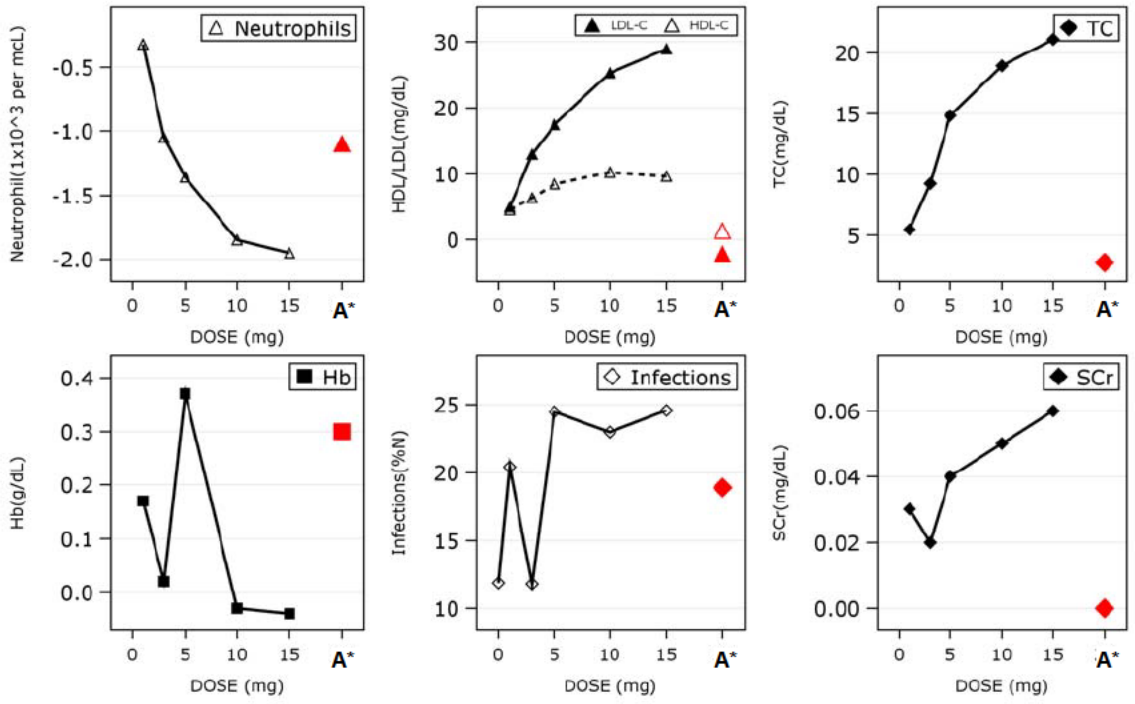


Figure 18: Dose-response relationship for safety endpoints from study 1035. Except infections all other endpoints are shown as placebo adjusted change from baseline to week 12 (delta baseline). Infections are reported as percent incidence at week 12. Active comparator adalimumab is shown as A* on x-axis and in red color symbol in graphs

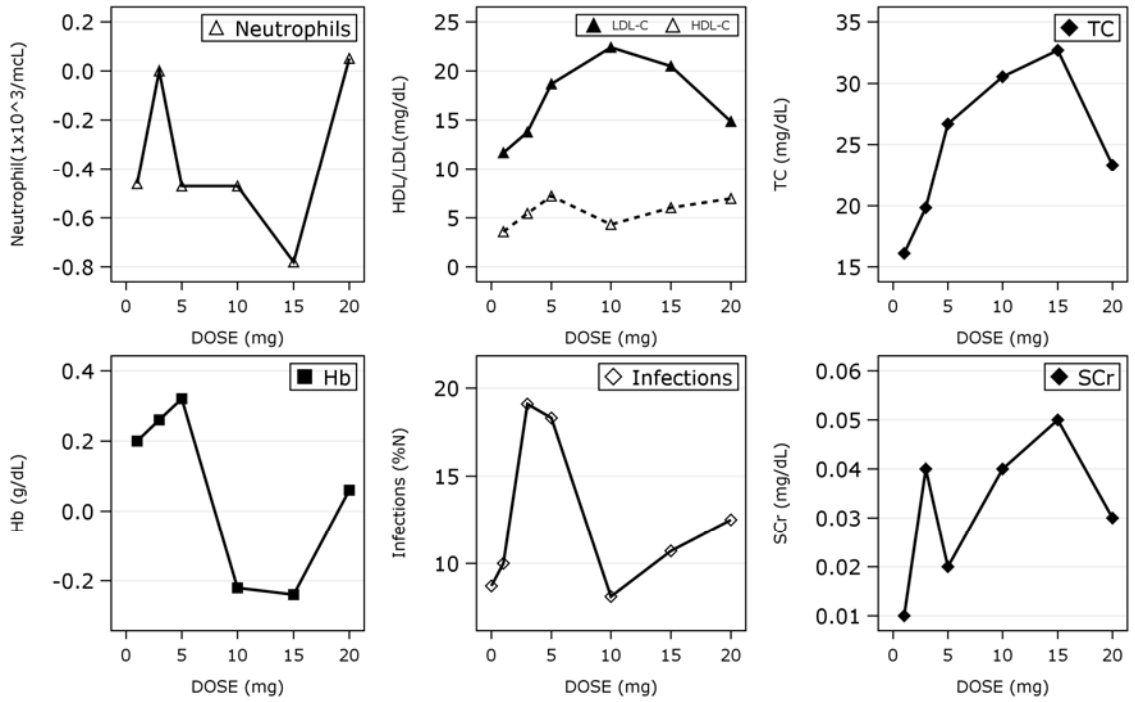
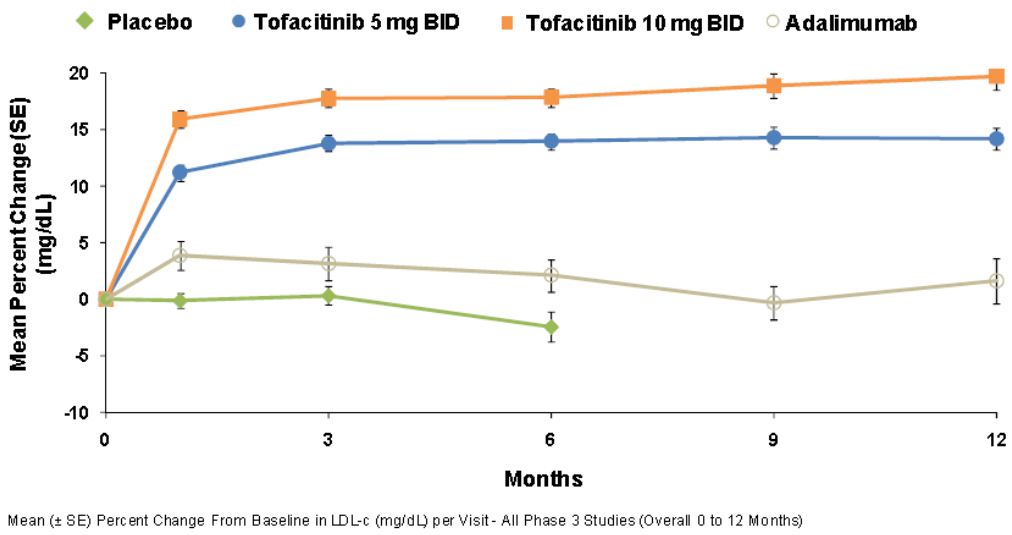


Figure 19: Dose-response relationship for safety endpoints from study 1025. Except infections all other endpoints are shown as placebo adjusted change from baseline to week 12 (delta baseline). Infections are reported as percent incidence at week 12. Except 20 mg QD all other doses were given in BID regimen

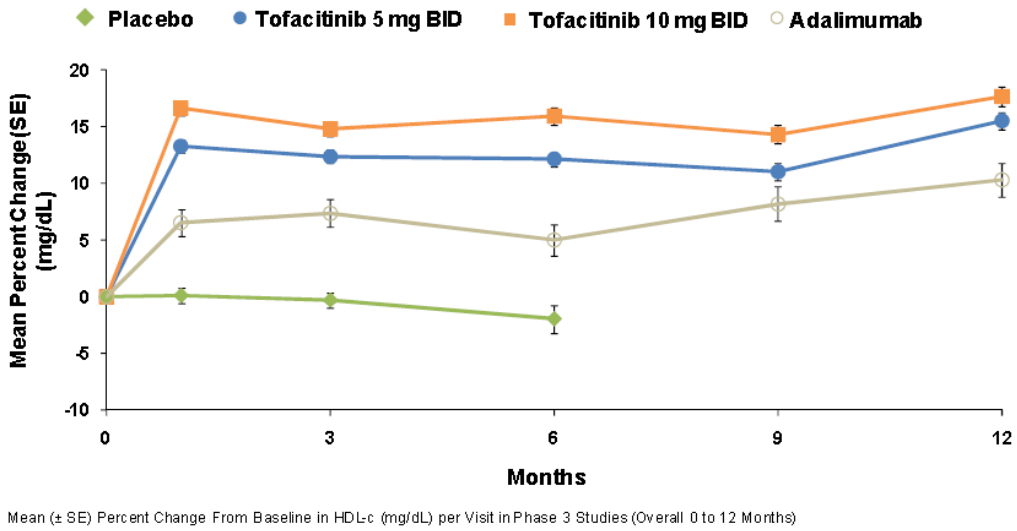
The longitudinal changes in key laboratory endpoints between 0 to 12 months duration based on data from all phase 3 trials are shown in Figure 20, Figure 21, Figure 22, Figure 23, Figure 24 and Figure 25. Similar to phase 2 studies dose dependent increase was observed for LDL, HDL, serum creatinine and dose dependent decrease was observed for neutrophil counts. Maximum changes in these laboratory endpoints occurred by weeks 2 to 4, which then remained almost stable for the complete duration of treatment (i.e., up to 12 months). For hemoglobin levels, increase was observed for both 5 mg BID and 10 mg BID dose compared to placebo; however, increase in hemoglobin for 5 mg dose was relatively higher than 10 mg dose, indicating to an inconsistent dose response behavior. Note that this trend was similar to that observed in Phase 2 studies A3921025 and A3921035. For lymphocytes, levels increased initially followed by decline for both 5 and 10 mg BID dose with less separation between two dose levels.



BID=twice daily; LDL-c=low density lipoprotein cholesterol; SE=standard error

Figure 20: Mean (±SE) Percent Change From Baseline LDL-c (mg/dL) per Visit – All Phase 3 Studies (Overall 0 to 12 Months)

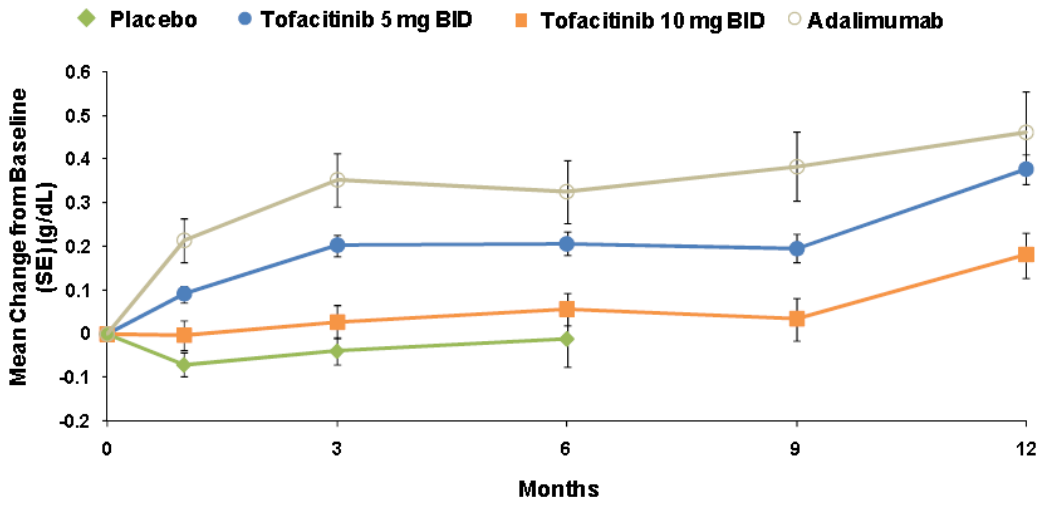
(Source: Figure 48, Pfizer Tofacitinib Advisory Committee Meeting Briefing Document, Dated May 9, 2012)



BID=twice daily; HDL-c=high density lipoprotein cholesterol; SE=standard error.

Figure 21: Mean (±SE) Percent Change From Baseline HDL-c (mg/dL) per Visit – All Phase 3 Studies (Overall 0 to 12 Months)

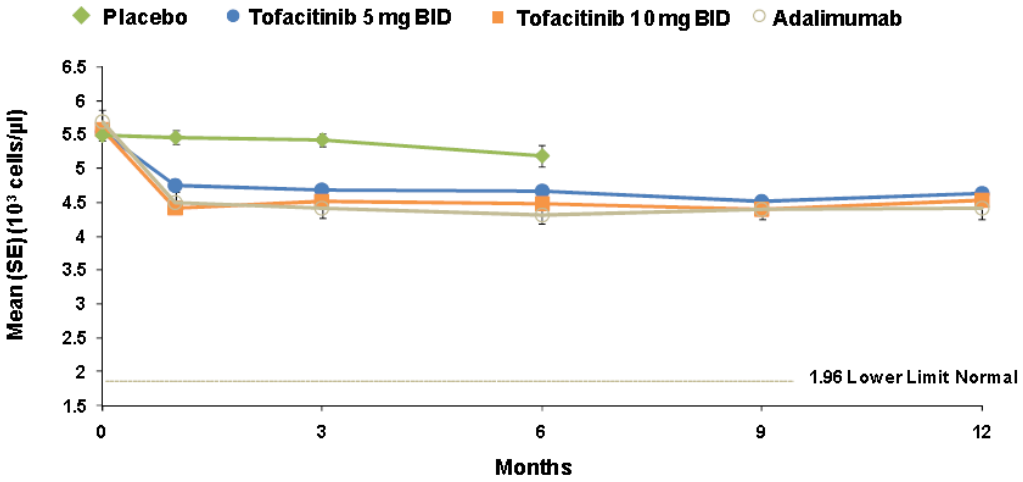
(Source: Figure 49, Pfizer Tofacitinib Advisory Committee Meeting Briefing Document, Dated May 9, 2012)



BID=twice daily, SE=standard error.

Figure 22: Mean (± SE) Change from Baseline in Hemoglobin (g/dL) in Phase 3 Studies (0 to 12 Months)

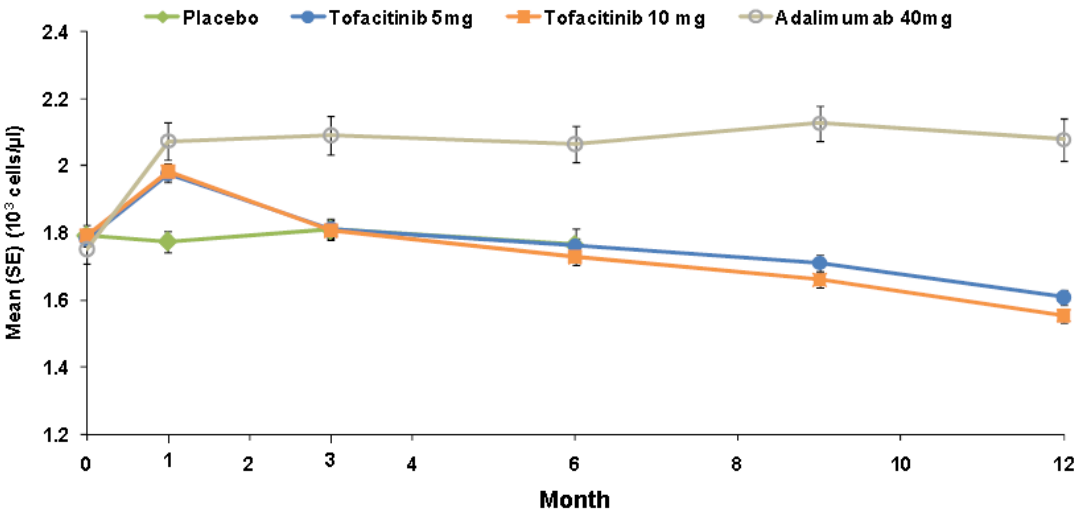
(Source: Figure 52, Pfizer Tofacitinib Advisory Committee Meeting Briefing Document, Dated May 9, 2012)



BID=twice daily; SE=standard error.

Figure 23: Mean (±SE) Neutrophil Levels in Phase 3 Studies (0 to 12 Months)

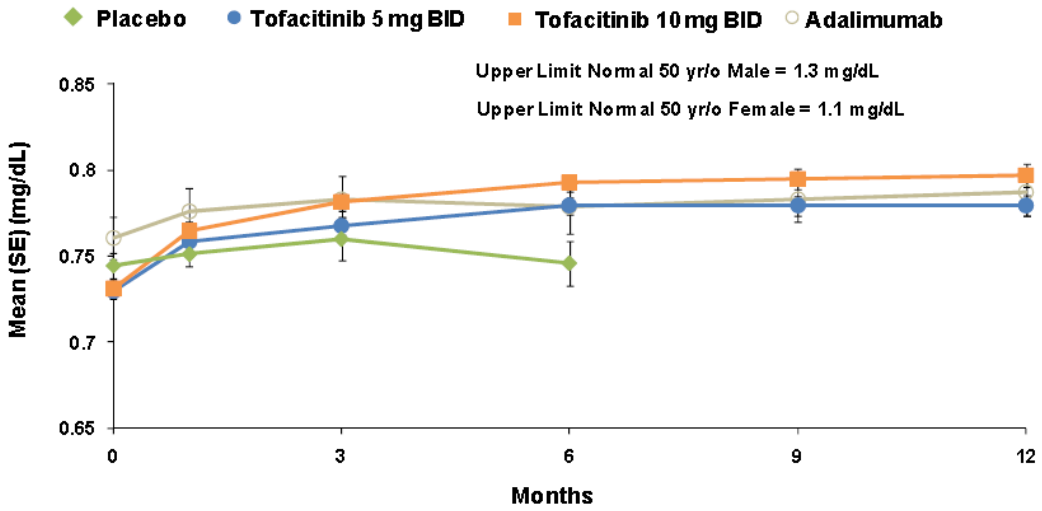
(Source: Figure 53, Pfizer Tofacitinib Advisory Committee Meeting Briefing Document, Dated May 9, 2012)



SE=standard error

Figure 24: Mean (±SE) Lymphocyte Levels in Phase 3 Studies (0 to 12 Months)

(Source: Figure 54, Pfizer Tofacitinib Advisory Committee Meeting Briefing Document, Dated May 9, 2012)



SE=standard error

Figure 25: Mean (±SE) Serum Creatinine Levels in Phase 3 Studies (0 to 12 Months)

(Source: Figure 56, Pfizer Tofacitinib Advisory Committee Meeting Briefing Document, Dated May 9, 2012)

1.1.4. Is the dose and dosing regimen selected consistent with the known Exposure-Response relationship?

Yes, the selection of dose and dosing regimen for phase 3 trials was consistent with the known dose response relationship for efficacy and safety. Note that a lower dose of 3 mg BID was also efficacious in study A3921025 and A3921035 but was not further

evaluated in Phase 3 clinical trials. The preclinical and clinical data used to support the dose selection and mechanistic reasoning in support of use of hemoglobin as safety marker in dose selection are discussed below:

A. Preclinical basis

Sponsor selected BID dosing regimen for optimization in clinical program; selection of which was based on preclinical studies in mouse collagen-induced arthritis (CIA) model. In this model QD and BID dosing regimen were tested. Comparison of efficacious concentrations with whole blood IC_{50} estimates for inhibition of various JAK dependent cytokines suggested that effective modulation of the inflammatory response through JAK1/3 did not require continuous coverage (i.e., plasma tofacitinib concentrations in excess of IC_{50}) of the target over the day. In these studies, the predicted tofacitinib dose to achieve 50% effectiveness (ED_{50}) in animal models for BID vs. QD dosing regimen were 6-12.8 mg/kg and 33.5-40.5 mg/kg, respectively. BID dosing was anticipated to provide concentrations higher than the IC50 for JAK1/3 inhibition for 12-13 hrs while this duration was 8.5-11 hrs for QD dosing. These data appears to be the basis for selection of BID dosing regimen for further optimization in clinical program. However, note that while it is logical to select the doses and dosing regimen based on preclinical information, it may not necessarily translate into a clinically relevant dosing. Also this preclinical information does not provide any information about safety of tofacitinib.

B. Clinical basis

Based on results from preclinical studies, sponsor designed the clinical program to optimize the BID dosing regimen. A total of 5 Phase 2 dose ranging studies were conducted, each of which evaluated more than one dose levels of tofacitinib in RA patients ranging from 1 to 30 mg for duration of 6 to 24-weeks. However, dose selection for Phase 3 studies was primarily based on study 1025, because design of this study was close to the anticipated real life use scenario for tofacitinib (i.e., use with background methotrexate treatment) and data were available from a relatively longer duration.

Sponsor analyzed the data from study 1025 to evaluate the probability of achieving the target efficacy and safety events. In terms of efficacy, dose selection was aimed at optimizing the response for ACR20, ACR50, and ACR70 endpoints by targeting placebo adjusted response rates at week 12 of at least 20%, 20%, and 15%, respectively. In terms of safety, only hemoglobin levels were considered in making the decision about dose based on data from study 1025, with target event of interest defined as <5% placebo adjusted incidence rate of severe anemia through 24 weeks. Where, severe anemia was defined as >2 g/dL decrease in hemoglobin from baseline or an absolute hemoglobin level of <8 g/dL. Other laboratory markers were not considered because of lack of consistency in dose-response relationship, as shown in Figure 4, with an exception for lipid parameters. Changes in lipid levels were not considered for dose selection because management of them would require individual patient specific considerations.

Probabilities of achieving the target effects are shown in **Error! Reference source not found.**. As shown in this figure, maximum probability of ACR20 target effect was reached by approximately 10 mg BID dose and an additional benefit was observed by

increasing the dose from 5 mg to 10 mg BID. For ACR70, the probability of achieving target effect for 10 mg BID dose was approximately 80%, which provided additional benefit over 40% probability achieved with 5 mg BID dose.

In terms of safety, the probability of <5% incidence of anemia was 100% with 5 mg dose which reduced to about 60% for 10 mg dose.

Overall, an approximately greater than 50% probability of achieving the target effect for efficacy and safety was obtained with both 5 mg BID and 10 mg BID doses. Therefore, these doses were selected for further evaluation in Phase 3 trials.

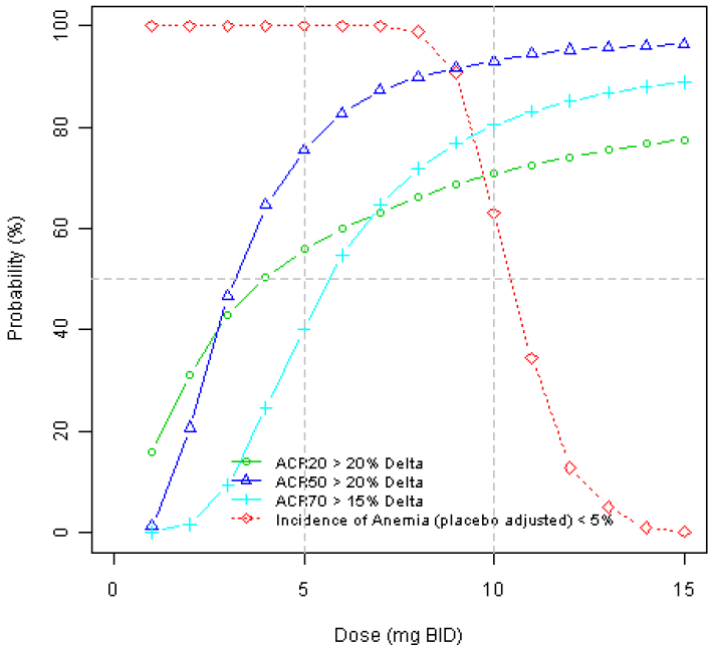


Figure 26: Probability of Achieving Target Effects for Efficacy (ACR20, ACR50 and ACR70 Response Rates) and Safety (Anemia) Endpoints Based on Dose-Response Modeling of A3921025 Data

(Source: Figure 3, study-pmar-00223 report/ Page 14)

C. Pharmacodynamic response data supporting selection of dosing frequency

Selection of the BID dosing frequency was also supported by a relatively longer pharmacodynamic half-life compared to pharmacokinetic half-life. Pharmacodynamic effects and safety of tofacitinib in rheumatoid arthritis patients were assessed for up to 6 weeks after cessation of treatment in the dose-ranging study A3921019. 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**Error! Reference source not found.**), indicating prolonged pharmacodynamic residual activity compared to short half-life of ~3 hrs.

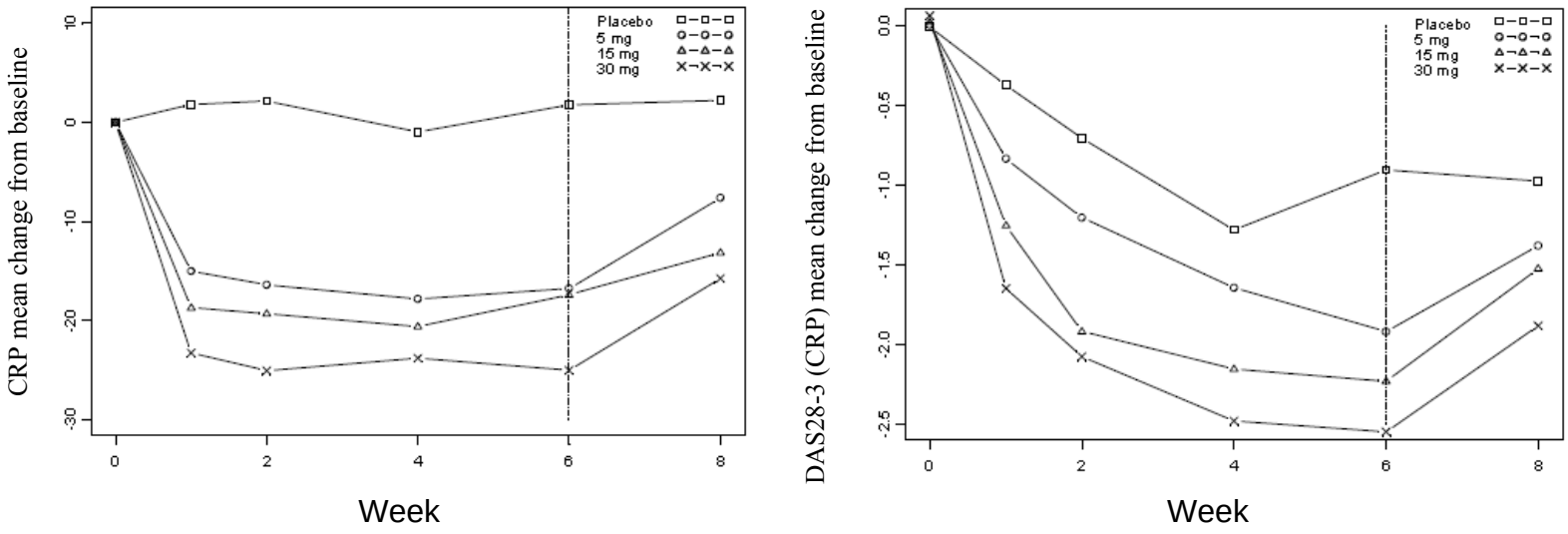


Figure 27: Time Course of Changes in CRP and DAS28-3(CRP) in Study A3921019

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

D. Mechanistic reasoning for selection of safety markers to support dose selection

If we evaluate the mechanistic rational for use of hemoglobin levels to support dose selection, based on available data about mechanism of action, tofacitinib's effect on hematopoiesis or hemoglobin levels is an outcome of off-target effect on JAK2 protein.

A more direct indicator of tofacitinib's activity on JAK1/3 proteins is the effect on CD4+ cells, which is also thought to be the mechanism of action for tofacitinib's activity in rheumatoid arthritis[3]. However, no dose-dependent changes in CD4+ cell counts were observed in data collected from two Phase 2 studies A3921019 and A3921035 after 6-week and 24-week treatment with tofacitinib, respectively (Figure 32). Therefore, changes in CD4+ counts, although mechanistically appear to be a better marker of tofacitinib activity, could not be used to support dose selection.

E. Comparability of Phase 2 and Phase 3 results

The results of Phase 3 clinical trials confirmed that both 5 mg BID and 10 mg BID dose were indeed better than placebo for ACR20, ACR50, and ACR70 endpoints, and durability of effect was seen for at least one year. To check how results from Phase 2 trials, which were used to select doses for Phase 3 studies, panned out in Phase 3 trials,

[3] Keisuke Maeshima et al. The JAK Inhibitor Tofacitinib Regulates Synovitis Through Inhibition of Interferon-_ and Interleukin-17 Production by Human CD4+ T Cells. *Arthritis and Rheumatism*. Vol 64, No 6, June 2012, pp 1790-1798

we compared the response rates and safety from Phase 3 trials with that observed in Phase 2 studies. The month 6 responses from Phase 3 Scan (A3921044), Sync (A3921046) and Standard (A3921064) studies and month 3 responses from Phase 3 Step (A3921032) study were in agreement with the week 12 response from Phase 2 study A3921025 (

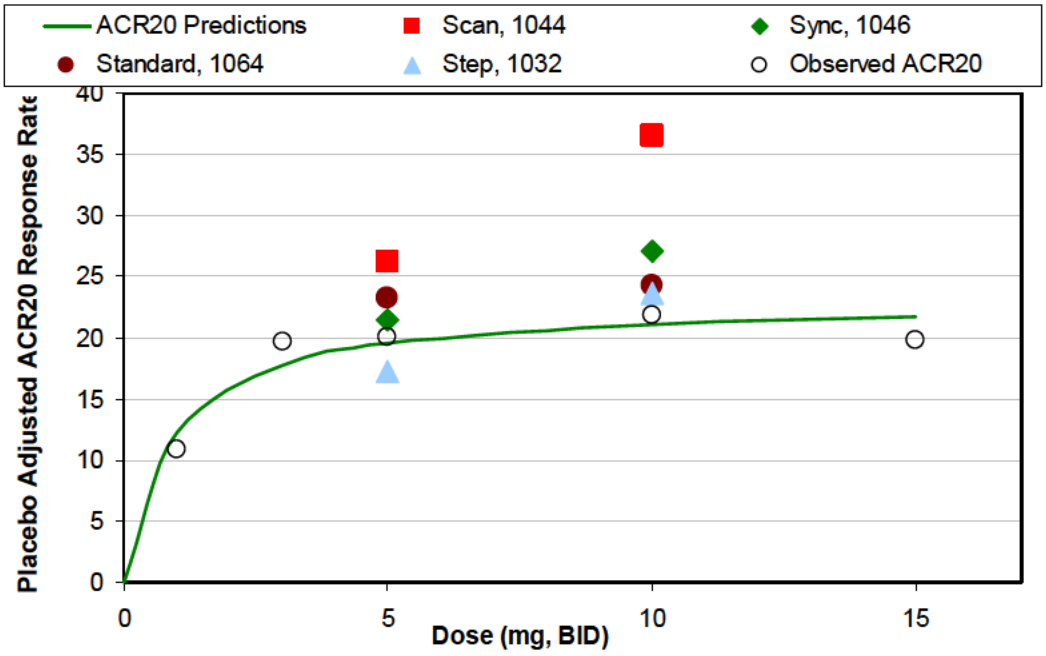
Figure 28, Figure 29 and

Figure 30), which confirmed that dose selection based on data from study A3921025 was appropriate. For further discussion on efficacy for ACR20, ACR50, ACR70 endpoints and effect on radiographic endpoints (i.e., preservation of structural damage) in Phase 3 trials, please refer to biostatistics review by Dr. Yongman Kim and clinical review by Dr. Nikolay Nikolov.

On the safety side, based on data from Phase 3 studies changes in hemoglobin response were not dose related. The 5 mg dose had higher increase in hemoglobin from baseline compared to 10 mg dose, for which mean change in hemoglobin was almost close to zero. This was consistent with the trend observed in Phase 2 studies A3921025 and A3921035, where an inverted U shape relationship was observed for absolute change in hemoglobin with dose. In study A3921025, 10 mg dose had drop in hemoglobin from baseline while 5 mg dose had no change or increase from baseline at week 12 (Figure 19) and week 24 (data not shown). This also confirms that use of hemoglobin data from study A3921025 to support dose selection was appropriate. The inverted U relationship for change in hemoglobin may be because of combined effect of tofacitinib on hematopoietic cells and on rheumatoid arthritis disease (which in turn influences hemoglobin levels).

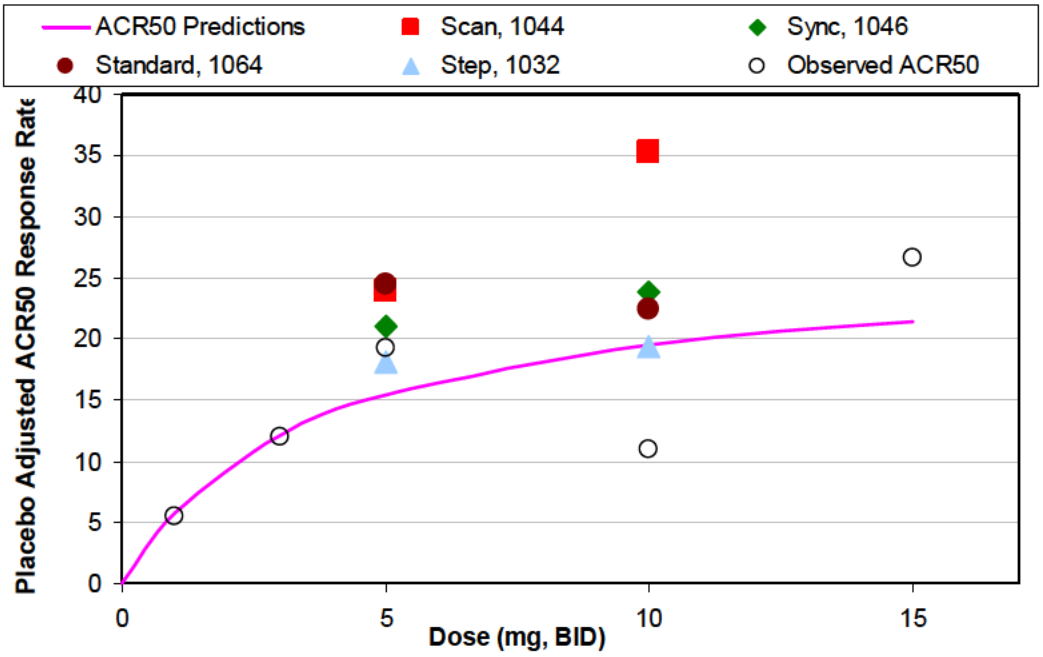
Among other safety markers, in Phase 3 trials, dose-dependent changes were seen in LDLC, HDLC, serum creatinine and neutrophil counts which were consistent with the trends observed in Phase 2 studies.

In Phase 3 trials, a dose- and time-dependent increase in exposure-adjusted rate of malignancy was observed, which was not possible to evaluate based on Phase 2 data because of shorter duration for those studies. Also, in Phase 3 trials, exposure-adjusted rate of opportunistic and serious infections were higher for 10 mg BID dose than 5 mg BID dose in randomized controlled period and/or in long-term extension period. To explore a possible mechanism for dose-dependency in infections, dose-response for T-cells and CD4+ cells was evaluated based on data from Phase 2 studies, which is discussed in response 1.1.5 (Page 59). For further information on safety evaluation for tofacitinib 5 and 10 mg doses from Phase 3 studies, please refer to biostatistics review by Dr. Yongman Kim and clinical review by Dr. Nikolay Nikolov.



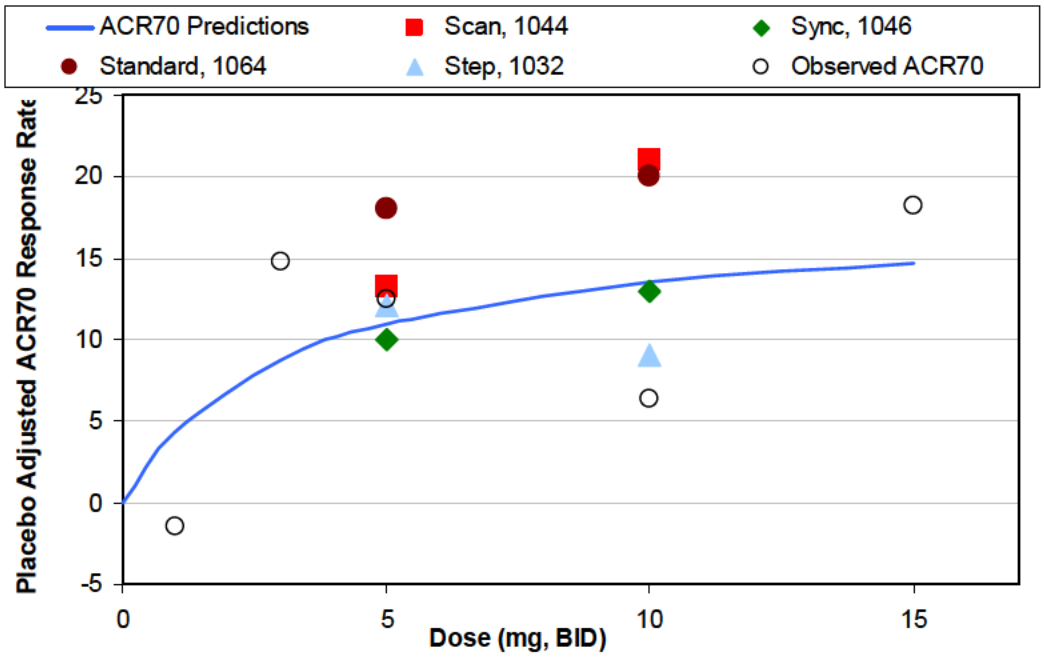
(Primary time point is Month 6 for Scan (A3921044), Sync (A3921046) and Standard (A3921064) studies and Month 3 for the Step (A3921032) study)

Figure 28: Comparison of model predicted placebo adjusted ACR20 response rate at week 12 based on study A3921025 with the ACR20 response rate observed in Phase 3 studies



(Primary time point is Month 6 for Scan (A3921044), Sync (A3921046) and Standard (A3921064) studies and Month 3 for the Step (A3921032) study)

Figure 29: Comparison of model predicted placebo adjusted ACR50 response rate at week 12 based on study A3921025 with the ACR50 response rate observed in Phase 3 studies



(Primary time point is Month 6 for Scan (A3921044), Sync (A3921046) and Standard (A3921064) studies and Month 3 for the Step (A3921032) study)

Figure 30: Comparison of model predicted placebo adjusted ACR70 response rate at week 12 based on study A3921025 with the ACR70 response rate observed in Phase 3 studies

1.1.5. What are the characteristics of the exposure-response relationship for pharmacodynamic markers?

Among pharmacodynamic markers, effect of CP-690,550 on T-cells, CD4+ cells, CD8+ cells, CD16/56+ cells, CD19+ cells, C-reactive protein (CRP), and immunoglobulins (IgG, IgA, IgM) are discussed below in subheadings A, B, C, and D.

A. Effect of CP-690,550 on total T-cell (CD3+) and CD4+ cell counts

Dose-dependency of changes in CD3+ and CD4+ T cell counts was evaluated to explore the potential mechanism for higher occurrence of exposure-adjusted rate of opportunistic infections with 10 mg dose compared to 5 mg dose. CD3+ or total T-cell counts were chosen because tofacitinib is thought to have a direct effect on T-cell pathways by its

JAK1/JAK3 inhibitory effect. CD4+ T cell counts were chosen because the pattern of infections was similar to the acquired T-cell immunodeficiency, which is manifested by deficiency in CD4+ cell counts. Dose-response relationships were visually assessed via box plots of percent change from baseline in cell counts at the end of the treatment period.

CD3+ cell counts were measured in three Phase 2 studies, A3921019, A3921025 and A3921035. No trend of dose-dependency was observed for % change from baseline in CD3+ cell counts across doses ranging from 0 to 30 mg (Figure 31).

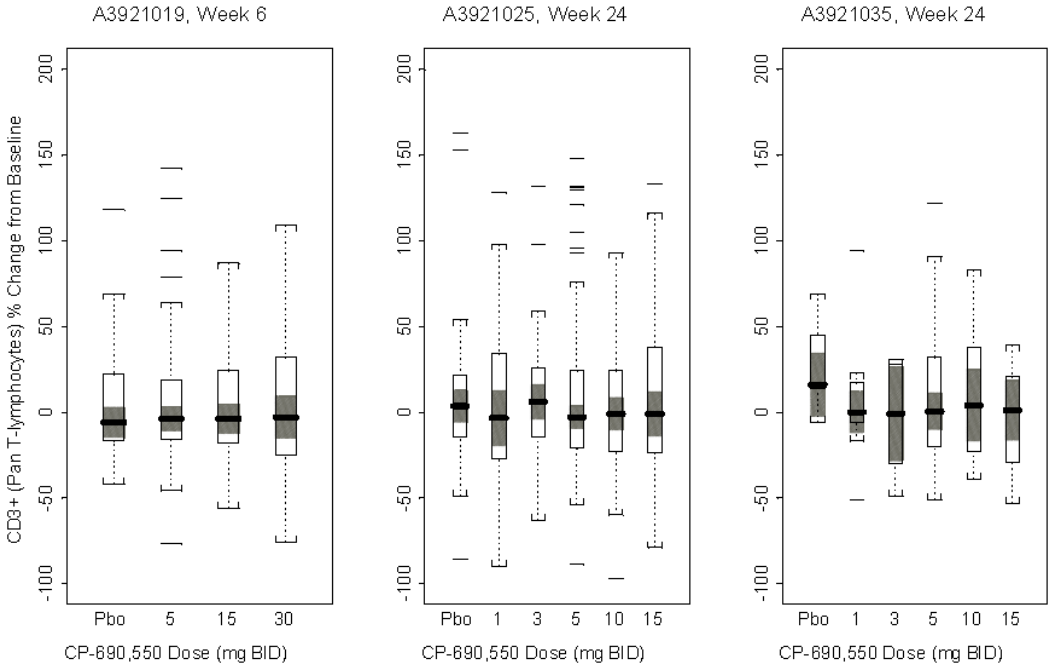


Figure 31: Percent change from baseline in CD3+ counts in RA patients

(Source: Figure S1, study report-pmar-00187/Page 6)

CD4+ cell counts were only collected in two Phase 2 studies, A3921019 and A3921035. Change from baseline in CD4+ cell counts across different dose levels following 6 weeks and 24 weeks treatment with tofacitinib are shown in Figure 32. No trend of dose-dependent change in CD4+ counts from baseline was observed, suggesting that CD4+ counts may not be used to discriminate between doses and support dose selection. In fact visual comparison of spread from trial A3921035 shows that the percent decline from baseline in CD4+ cell count was larger for 5 mg BID dose group than the 10 mg BID dose group, which is opposite to the trend observed for opportunistic infections. These results indicate a functional rather than cytotoxic effect of tofacitinib on CD4+ T cells and also do not support the laboratory monitoring of CD4+ cell counts in clinical setting.

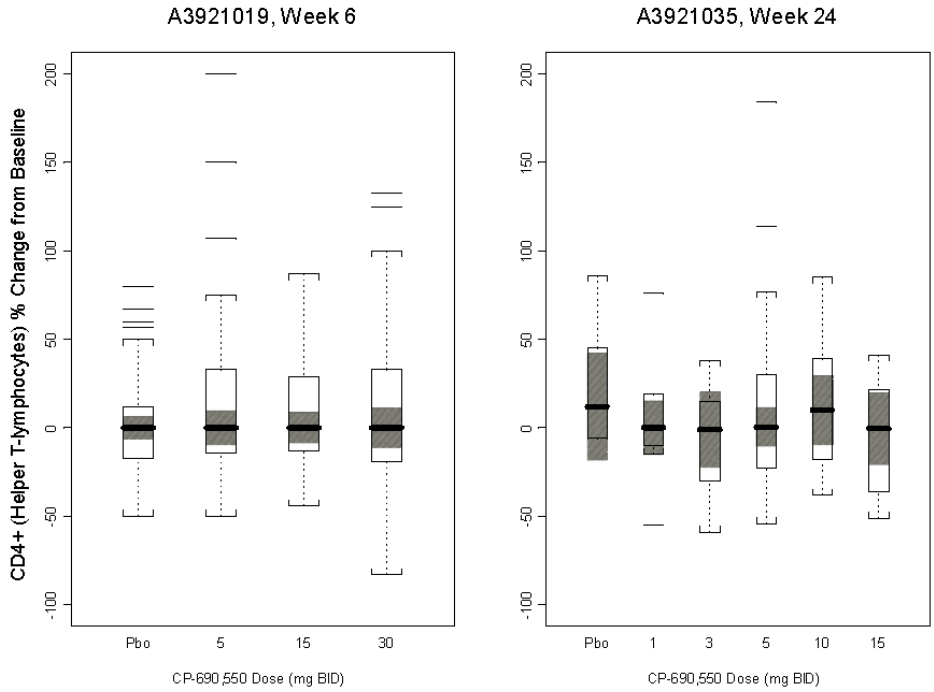


Figure 32: Percent change from baseline in CD4+ counts in RA patients

(Source: Figure S2, study report -pmar-00187/Page 7)

B. Effect of CP-690,550 on CD8+, CD16/56+ and CD19+ cell counts

In Phase 2 studies, CD8+, CD16/56+ and CD19+ cell counts were also measured. No dose dependency was observed for change in CD8+ cell counts after 6 or 24 weeks treatment with tofacitinib (Figure 33). In contrast, NK cell counts (CD16/+CD56+) showed a trend of dose-dependent decrease (Figure 34), and B cell counts (CD19+) showed a trend of dose-dependent increase (Figure 36) in all three Phase 2 studies.

Sponsor modeled the data for NK cell counts from studies A3921019, A3921025 and A3921035 using a longitudinal, non-linear, mixed-effect analysis. The model predicted mean NK cell counts were in agreement with the observed mean NK cell values as shown in Figure 35. This model estimated the NK cell elimination rate (i.e., K_{out} in the model) to be 0.049 day^{-1}. This K_{out} value translates into a half-life for NK cell decline of approximately 14 days (i.e., $t_{1/2}$=0.693/0.049) with a maximum decline (i.e., nadir) occurring in 4-5 half-lives, that is approximately 56-70 days or 8-10 weeks. Mean NK cell counts returned to baseline in 2-6 weeks after cessation of treatment as shown from observed data in study A3921019 (Figure 35).

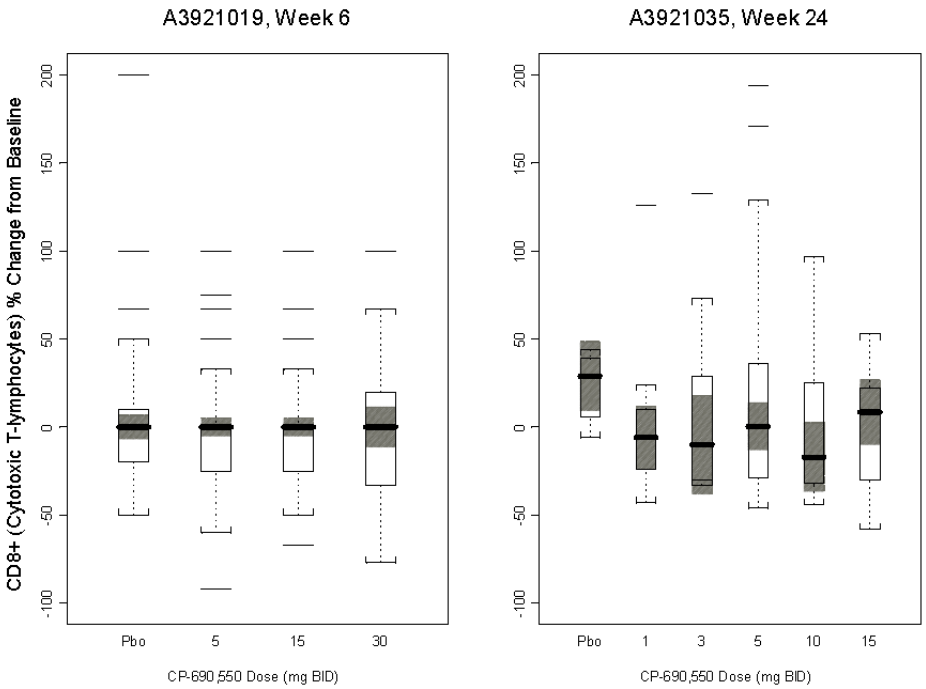


Figure 33: Percent change from baseline in CD8+ counts in RA patients

(Source: Figure S3, study report -pmar-00187/Page 8)

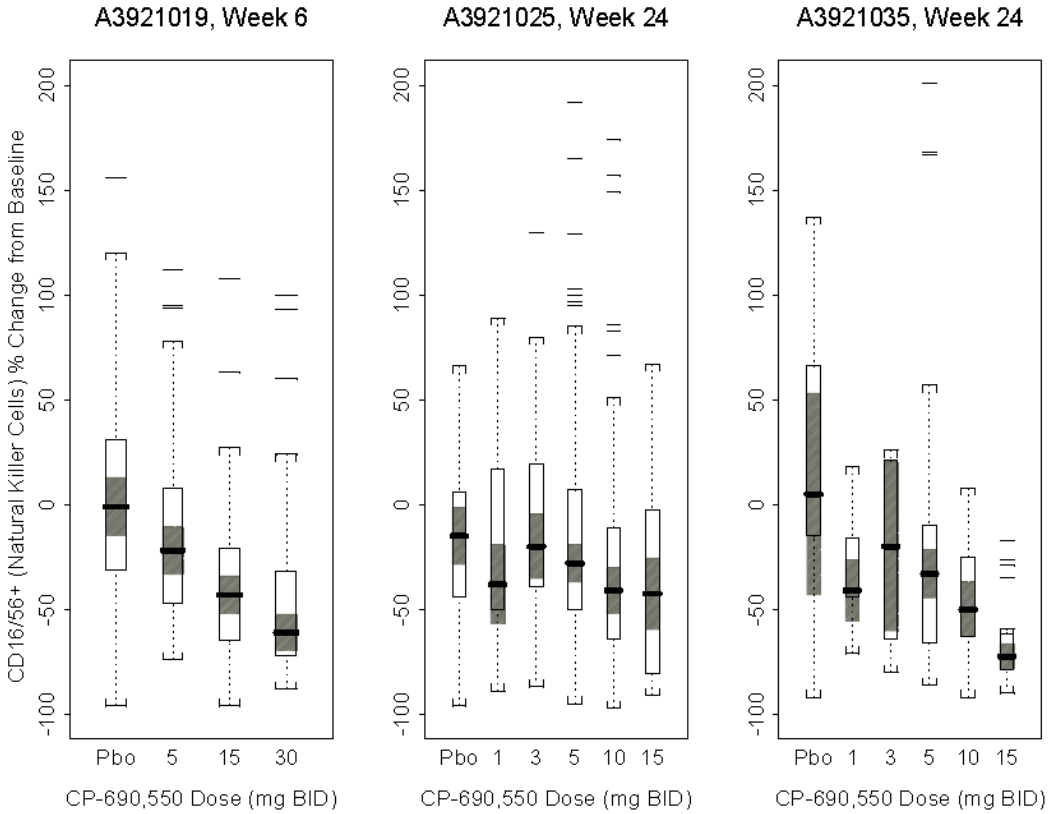


Figure 34: Percent change from baseline in CD16/56+ counts in RA patients

(Source: Figure S4, study report-pmar-00187/Page 9)

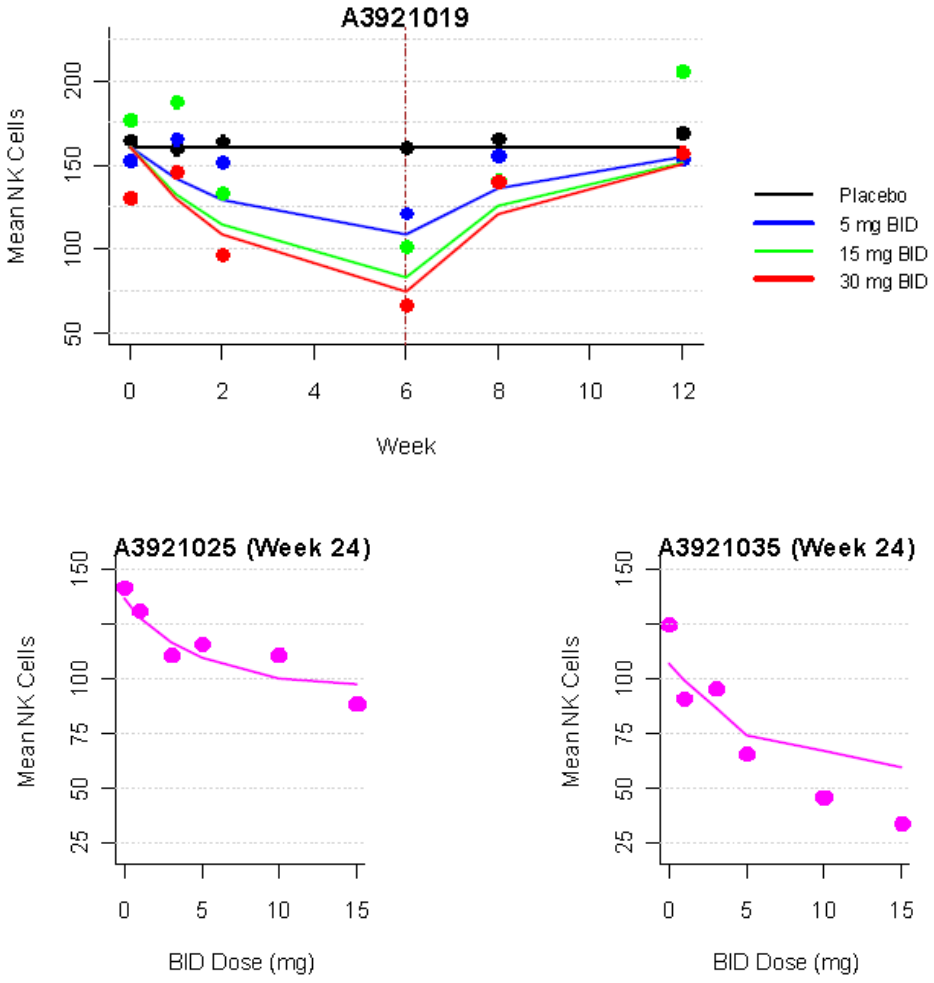


Figure 35: Observed mean CD16/56+ counts (Filled Circles) and Model Predictions (Lines) from Final Dose-Response Model for trial A3921019, A3921025 and A3921035

(Source: Figure 10, study report-pmar-00187/Page 47)

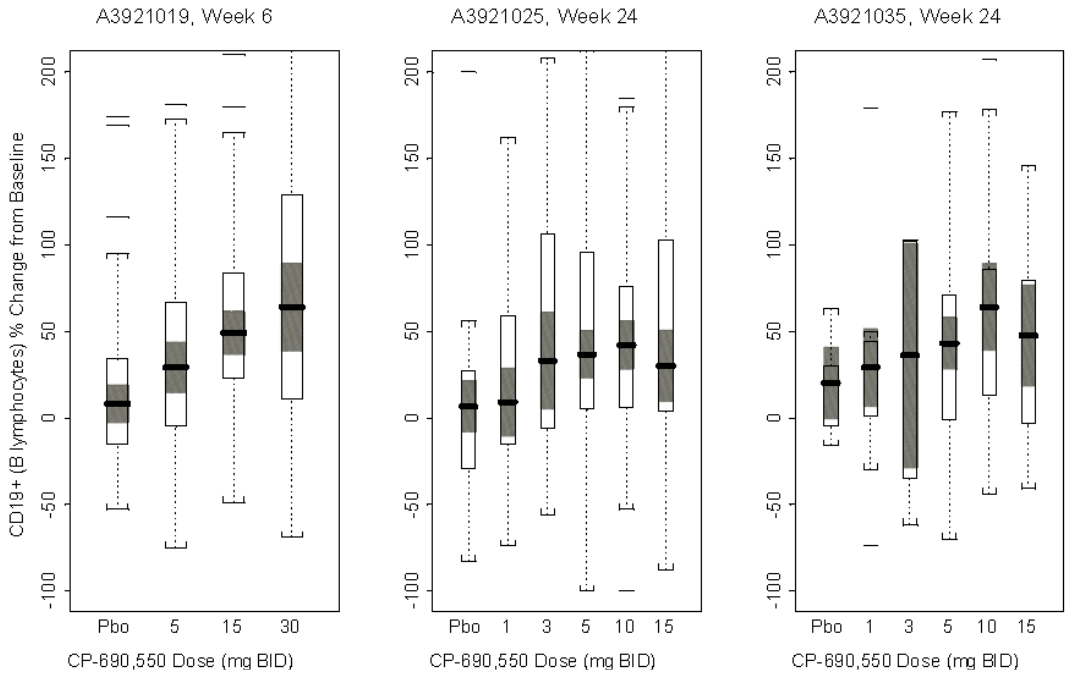


Figure 36: Percent change from baseline in CD19+ counts in RA patients

(Source: Figure S5, study report-pmar-00187/Page 10)

C. Effect of CP-690,550 on C-reactive protein (CRP) in RA patients

The time course and dose-response relationship for effect of CP-690,550 on CRP was assessed based on pooled analysis of Phase 2 studies A3920125, A3921035, A3921039 and A3921040 and is shown in Figure 37. Administration of CP-690,550 resulted in rapid and dose dependent reduction in CRP within 2 weeks of treatment, with minimal additional decrease beyond 2 weeks. The longitudinal observed data from study A3921019 as shown in **Error! Reference source not found.** also supports the same conclusions.

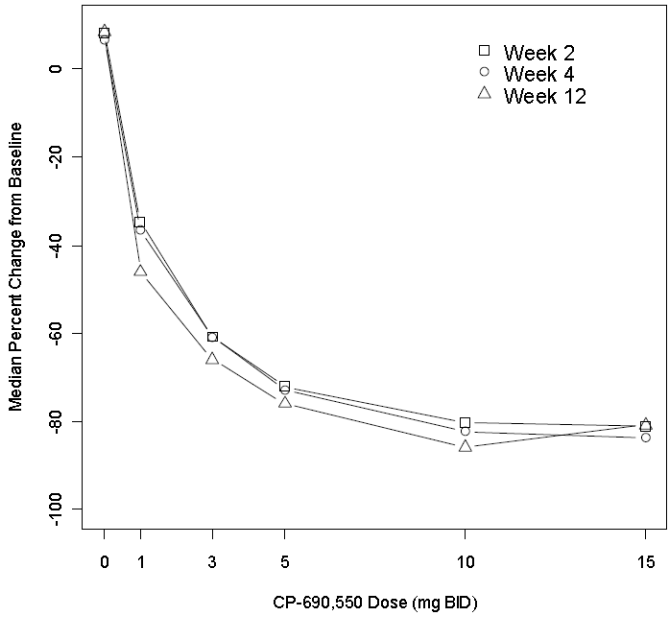
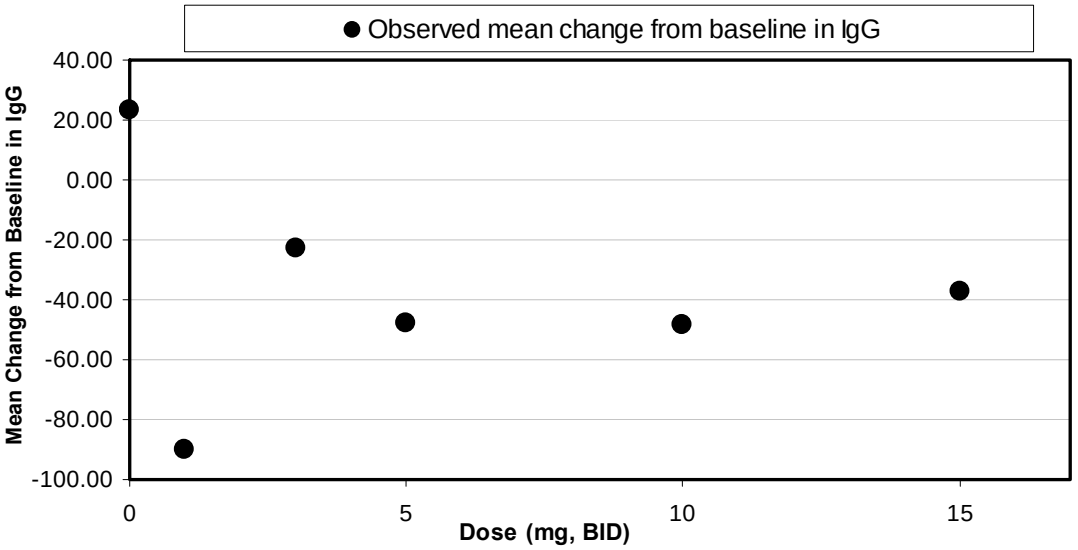


Figure 37: Effect of CP-690,550 on CRP in RA Patients Based on Pooled Analysis of Phase 2 Studies A3920125, A3921035, A3921039 and A3921040

(Source: Figure 1, study report-pmar-00223/Appendix 10/Page 110)

D. Effect of CP-690,550 on serum IgG, IgM, IgA antibodies in RA patients

A decline was observed in serum antibodies, IgG, IgM, and IgA, following treatment with tofacitinib for 24 weeks compared to placebo in study A3921025; however, these changes were small and not dose-dependent (Figure 38, Figure 39, Figure 40).



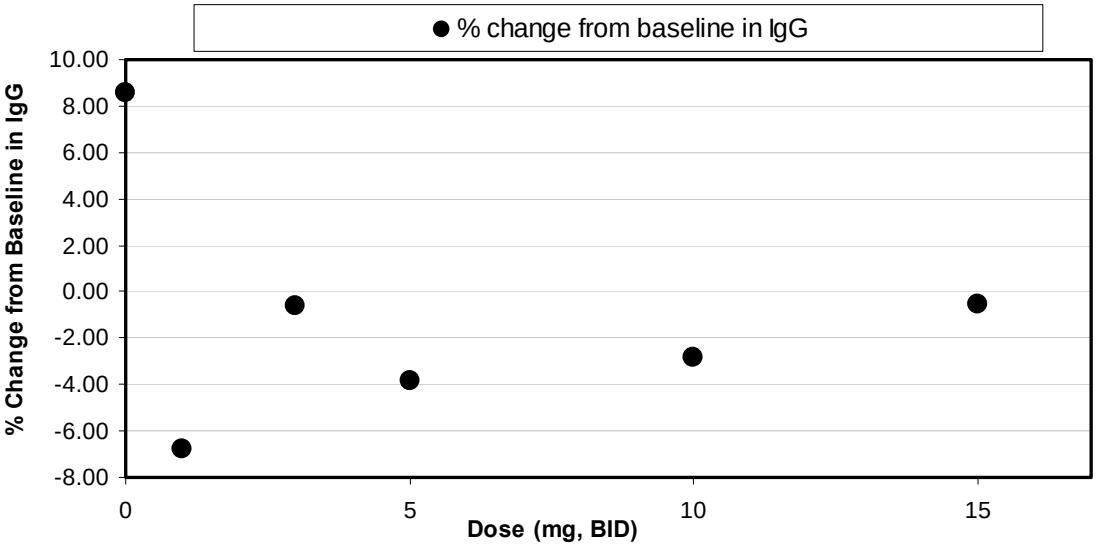
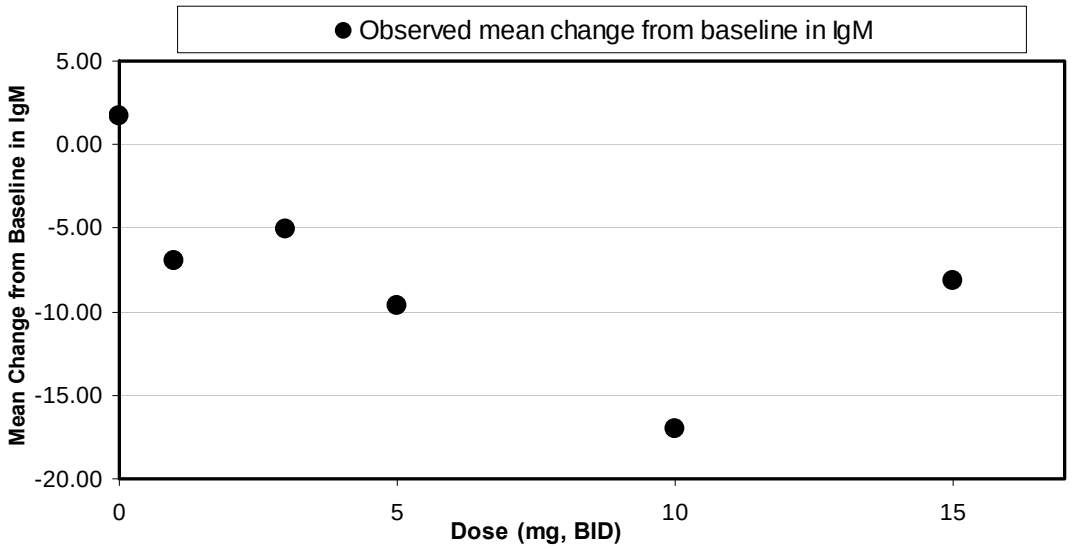


Figure 38: Mean observed and percent change (top and bottom figure, respectively) from baseline in total serum IgG following 24 week treatment with tofacitinib in study A3921025



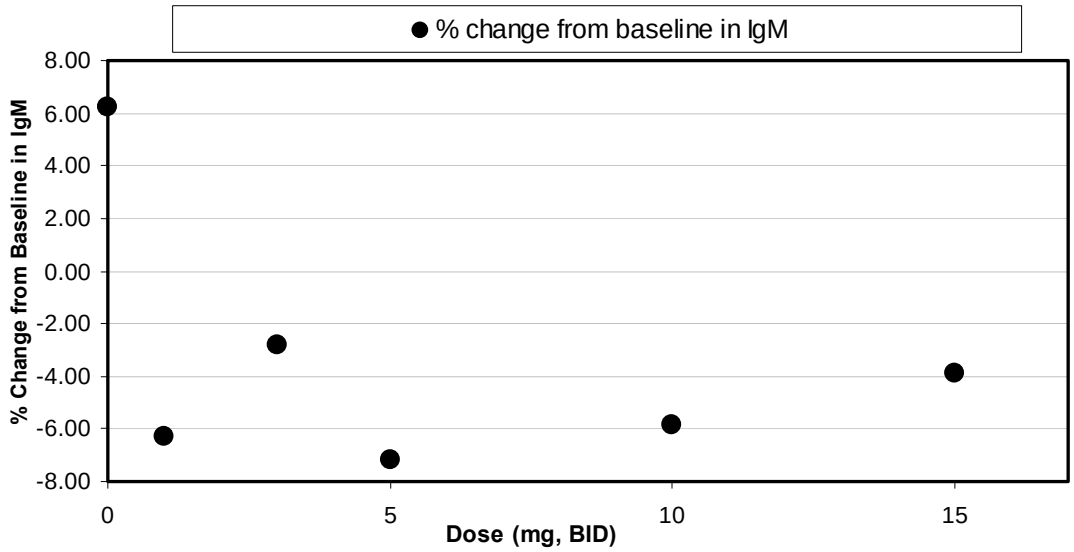
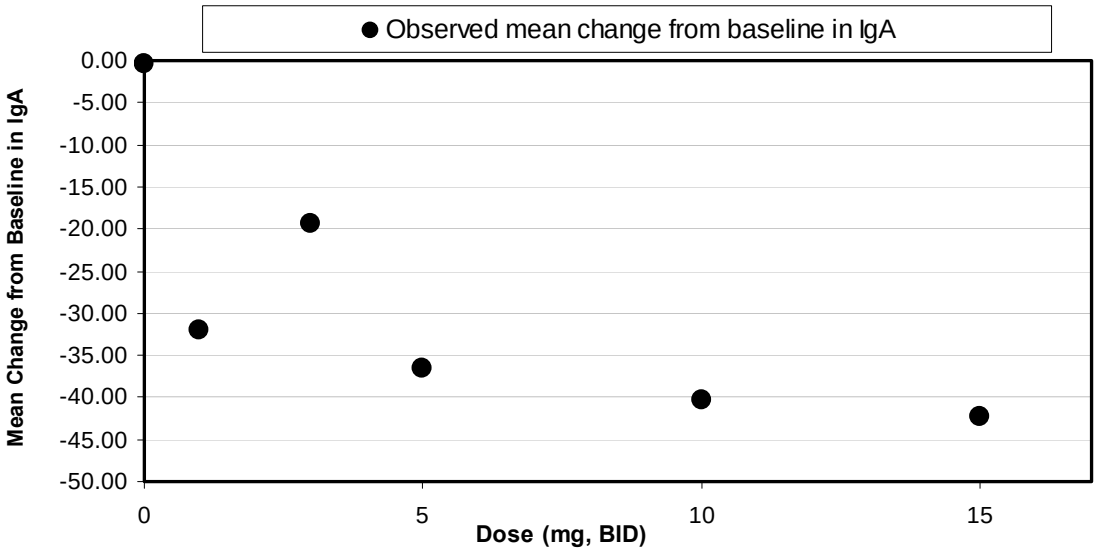


Figure 39: Mean observed and percent change (top and bottom figure, respectively) from baseline in total serum IgM following 24 week treatment with tofacitinib in study A3921025



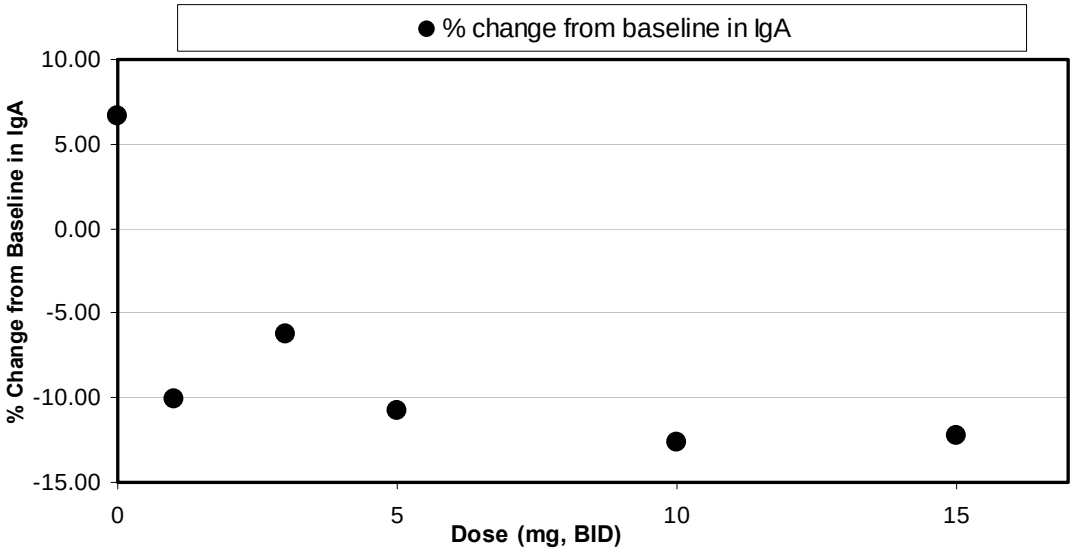


Figure 40: Mean observed and percent change (top and bottom figure, respectively) from baseline in total serum IgA following 24 week treatment with tofacitinib in study A3921025

1.2. Recommendations

NA

1.3. Label Statements

Following labeling statements are proposed in the label based on dose-response information. Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

2. PERTINENT REGULATORY BACKGROUND

CP-690,550 is an oral, potent, selective inhibitor of the Janus kinase (JAK) family of kinases (JAK1, JAK2, JAK3, and tyrosine kinase2) with a high degree of selectivity against other kinases in the human genome.

3. RESULTS OF SPONSOR'S ANALYSIS

The objectives of sponsor's population pharmacokinetic analysis were

• To characterize CP-690,550 PK in patients with RA.

• To identify any covariates that are important determinants of CP-690,550 exposure.

The overview of studies included in the population pharmacokinetic analysis is shown in Table 28 below.

The population pharmacokinetic analysis considered the 5 studies which comprised the Phase 2 program and included 6039 observations from 1070 patients. Doses ranged from 1 to 30 mg BID and 20 mg QD. The studies included 3 monotherapy studies (A3921019, A3921035 and A3921040) and 2 background methotrexate (MTX) studies (A3921025 and A3921039). The study population consisted of 183 males and 887 females with ages ranging from 18 to 81 years and weights ranging from 31.4 to 147 kg. There were 543 Caucasian, 19 African American, 386 Asian (360 Japanese), 107 Hispanic, and 15 subjects of Other race.

Table 28. Overview of Phase 2 Studies Used for Population PK Analysis

Study Number	Design Features	Treatments	Plasma Sampling
A3921019	Phase 2A, 6-week,double-blind, placebo-controlled, parallel group study	Placebo, 5, 15, and 30 mg BID	pre-dose samples on Day 0, and Weeks 1, 2 and 6. Post-dose samples at 1-3 h (Day 0 and Week 6), 4-5 h (Day 0).
A3921025	Phase 2B, 24-week, double-blind, placebo-controlled, parallel group study	Placebo, 1, 3, 5, 10, and 15 mg BID and 20 mg QD	pre-dose samples and 1, 2 and 4 h post-dose samples at Week 6 and 12.
A3921035	Phase 2B, 24-week, double-blind, placebo- and active-controlled, parallel group study	Placebo, 1, 3, 5, 10, and 15 mg BID and 40 mg Q2W adalimumab	pre-dose samples and 1, 2 and 4 h post-dose samples at Week 4 and 16.
A3921039	Phase 2, 12-week, double-blind, placebo-controlled, parallel group study in Japanese RA patients	Placebo, 1, 3, 5, and 10 mg BID, all treatments are add-on therapy with methotrexate	Samples at 1 hour and 5 minutes prior to dosing and 1 hour after dosing at Week 4 and at pre-dose, 30 minutes and 2 hours post-dose at Week 8.
A3921040	Phase 2, 12-week, double-blind, placebo-controlled, parallel group study in Japanese RA patients	Placebo, 1, 3, 5, 10, and 15 mg BID	Samples at 1 hour and 5 minutes prior to dosing and 1 hour after dosing at Week 4 and at pre-dose, 30 minutes and 2 hours post-dose at Week 8.

Source: Table 1 on page 16 in study-pmar-00178.pdf

The analysis was performed using nonlinear mixed effects modeling methodology as implemented in NONMEM® Version 7.1.2 (ICON Development Solutions, Ellicott City, MD). Models were developed on a computer grid with multiple compute nodes. Each node runs the Mac OS X operating system and utilizes the Intel® Fortran Compiler, version 11.1. Due to lack of adequate samples in the absorption phase, sponsor analyzed the data using the NONMEM subroutine ADVAN1 TRANS2 with the inclusion of a zero-order absorption duration (D1) parameter. Figure 41 **Error! Reference source not found.**shows the observed concentrations versus time stratified by dose for four of five studies. Plasma concentrations were sampled at various times throughout the dosing interval, with a majority of data points observed within 4 hours of dosing and another large grouping of sampling times between 10 and 14 hours

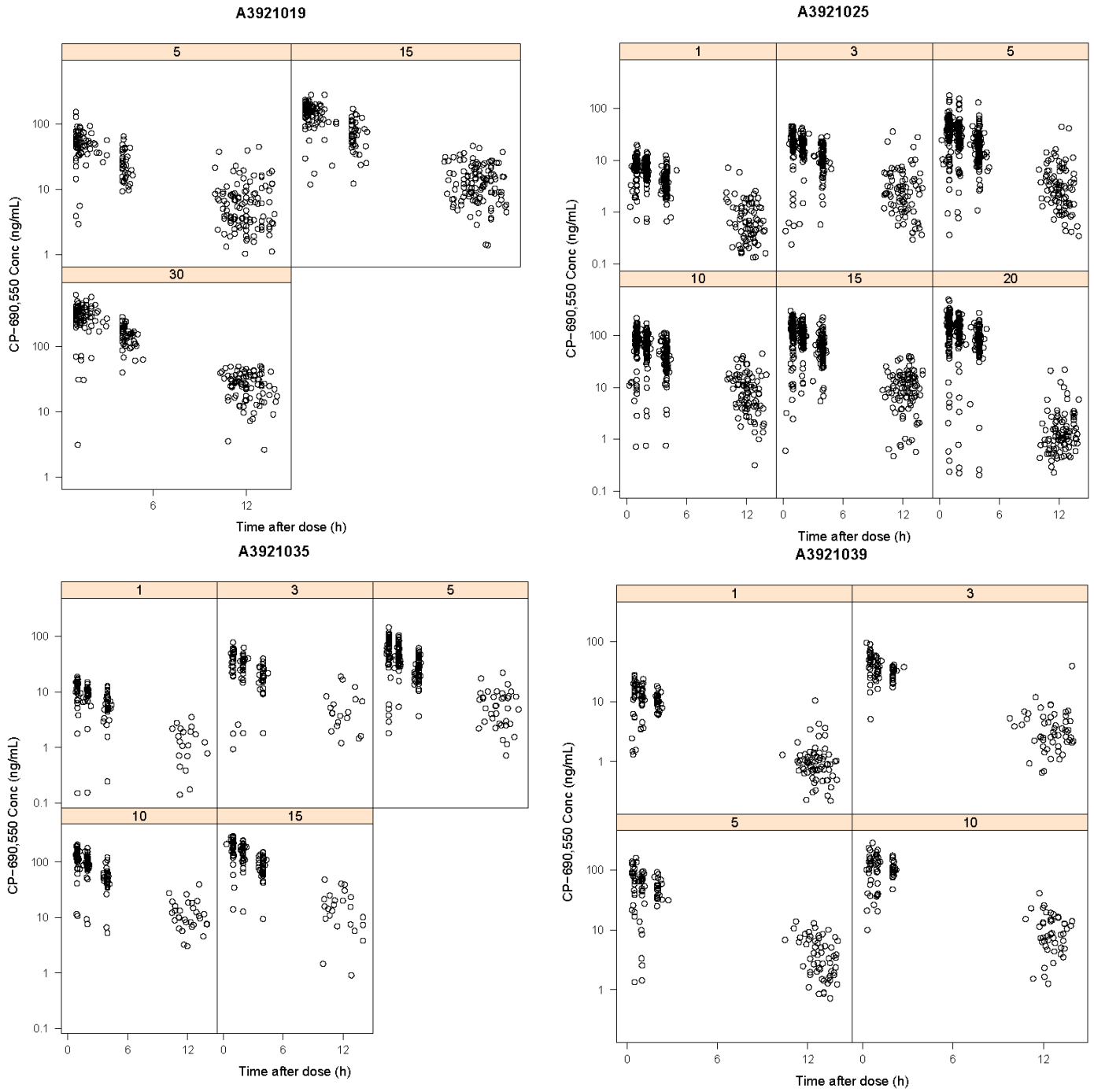


Figure 41: Observed CP-690,550 Concentrations versus Actual Time After Dose. Plots are presented for each study, stratified by CP-690,550 dose (mg)

(Source: adapted from Figure 1 on page 27 from study-pmar-00178.pdf)

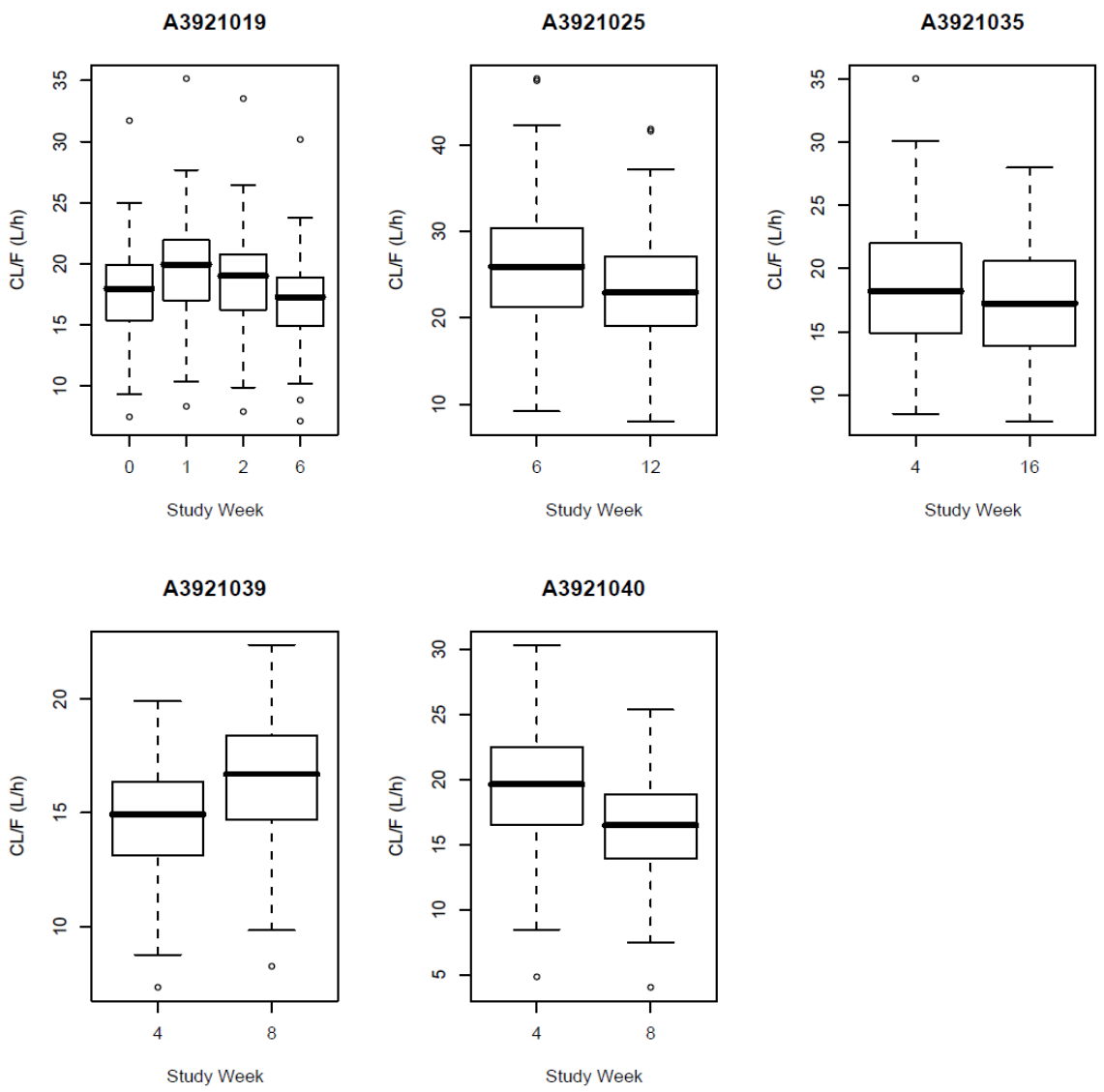
The base one-compartment model provided an adequate description of the data, as judged by visual inspection of diagnostic plots. The base model structural parameter estimates, presented in Table 29, were relatively precise. The typical estimates of CL/F and V/F from the base model were 20.6 L/h and 90.2 L with relative standard errors of < 2%. The zero-order absorption duration was 0.339 h with a relative standard error of 13.5%. Between-patient variability estimates for CL/F and V/F were 30.8% and 30.1% (coefficient of variation), respectively. Inter-occasion (or within-patient) variability in F was 22.9%. Residual variability in pre-dose and non-pre-dose concentrations were estimated to be 68.3% and 34.4%, respectively. Shrinkage estimates from the base model were 24.4% for CL/F and 31.4% for V/F random effects.

Table 29. Parameter Estimates from CP690,550 Base Population Pharmacokinetic Model (Run 500)

	Point Estimate	%RSE	IIV	IOV
CL/F	20.6 (L/h)	1.47	30.8 (CV%)	
V/F	90.2 (L)	1.70	30.1 (CV%)	
$D1$	0.339 (h)	13.5		
$F1$	1	$Fixed$		22.9 $(CV\%)$
Inter-individual Variance				
$\Omega^2_{CL/F}$	0.0951	10.5		
$\Omega^2_{CL/F-V/F}$	0.0357	26.3		
$\Omega^2_{V/F}$	0.0905	11.2		
Inter-occasion Variance				
Ω^2_{F1}	0.0524	19.3		
Residual Variance				
σ^2_{prop}	0.118	6.64		
$\sigma^2_{prop,trough}$	0.467	33.6		
Prop. Error CV	34.4 (CV%)			
Prop. Error CV (trough)	68.3 (CV%)			

Source: Table 6 on page 28 from study-pmar-00178.pdf

After the base model was developed, a separate model was constructed using the base model as a starting point with a separate CL/F term estimated for each study occasion. This was conducted to determine if CP-690,550 CL/F is time-dependent (e.g., auto-induction or inhibition of CL/F). CL/F estimates by study week are shown in Figure 42. Although some variation in CL/F is evident across study weeks, CL/F estimates were generally equivalent over time within each study. CL/F estimates were also consistent



Source: Figure 2 on page 29 from study-pmar-00178.pdf

Figure 42: CL/F empirical Bayes estimates vs. Study Week for the CP-690,550 Base Model

The influence of various prognostic factors such as age, renal function (CrCL), total body weight etc on clearance and volume of distribution were evaluated (Figure 43).

The final model equations (Source: Page 30 from study-pmar-00178.pdf) are shown below:

CRCL $\geq$ 80 mL/min:

$$\frac{CL}{F_i} = \theta_{CL} \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{\theta 4} \cdot \left(\frac{\text{AGE}_i(\text{years})}{55(\text{years})}\right)^{\theta 7} \cdot \theta 7^{\text{Female}}$$

$$\cdot\, \theta 9^{\text{AfricanAmerican}} \cdot \theta 10^{\text{Asian}} \cdot \theta 11^{\text{Hispanic}} \cdot \theta 12^{\text{OtherRace}} \cdot \theta 14^{\text{A3921025}} \cdot \exp^{\eta_{CL/Fi}}$$

CRCL $<$ 80 mL/min:

$$\frac{CL}{F_i} = \theta_{CL} \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{\theta 4} \cdot \left(\frac{\text{AGE}_i(\text{years})}{55(\text{years})}\right)^{\theta 7} \cdot \left(\frac{CRCL_i(\text{mL/min})}{80(\text{mL/min})}\right)^{\theta 17} \cdot \theta 7^{\text{Female}}$$

$$\cdot\, \theta 9^{\text{AfricanAmerican}} \cdot \theta 10^{\text{Asian}} \cdot \theta 11^{\text{Hispanic}} \cdot \theta 12^{\text{OtherRace}} \cdot \theta 14^{\text{A3921025}} \cdot \exp^{\eta_{CL/Fi}}$$

$$\frac{V}{F_i} = \theta_{VF} \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})}\right)^{\theta 15} \cdot \left(\frac{\text{AGE}_i(\text{years})}{55(\text{years})}\right)^{\theta 8} \cdot \exp^{\eta_{V/Fi}}$$

$$D1 = \theta_{D1}$$

$$F = 1 \cdot \exp^{\eta_{IOV}}$$

Parameter estimates from the final model are presented in Table 30. The typical estimates (90% CI) of PK model parameters for the reference covariate effects (Caucasian, Male, 70 kg, 55 years, CRCL $\geq$ 80 mL/min, non-study A3921025) were 18.4 (16.1, 23.0) L/h, 96.0 (92.4, 101) L and 0.352 (0.267, 0.408) h, for CL/F, V/F, and D1, respectively. Inter-individual variability (% CV) was reduced for CL/F (26.6%)) and V/F (26.0%) in the final model compared to the base model CL/F (30.8%) and V/F (30.1%) variance estimates.

Table 30. Parameter Estimates from CP690,550 Final Population Pharmacokinetic Model (Run 502)

	Point Estimate	%RSE	90% CI	IIV	IOV
CL/F	18.4 (L/h)	8.48	(16.1, 22.7)	26.6 (CV%)	
V/F	96.0 (L)	1.76	(92.8, 99.6)	26.0 (CV%)	
$D1$	0.352 (h)	12.0	(0.267, 0.410)		
$F1$	1	*Fixed*			23.0 $(CV\%)$
Inter-individual Variance					
$\Omega^2_{CL/F}$	0.0707	16.0	(0.0558, 0.0931)		
$\Omega^2_{CL/F-V/F}$	0.0112	86.3	(0.00052, 0.0314)		
$\Omega^2_{V/F}$	0.0674	13.7	(0.0518, 0.0807)		
Inter-occasion Variance					
Ω^2_{F1}	0.0528	20.8	(0.0371, 0.0878)		
Residual Variance					
σ^2_{prop}	0.118	6.57	(0.106, 0.132)		
$\sigma^2_{prop,trough}$	0.411	29.7	(0.166, 0.527)		
Prop. Error CV	34.4 (CV%)				
Prop. Error CV (trough)	64.1 (CV%)				

Source: Table 7 on page 32 from study-pmar-00178.pdf

The covariate parameter estimates are shown in Table 31. The 90% CI's for body weight, age, gender, and race (African American, Hispanic, and Asian) effects on CL/F were not distinguishable from the null value.

Table 31. Covariate Parameter Estimates from the CP-690,550 Full Population Pharmacokinetic Model (Run 502).

Parameter	Covariate	Estimate	%RSE	90% CI
CL/F	*Weight*	0.0427	292	$(-0.215, 0.268)$
CL/F	*Age*	-0.0629	135	$(-0.253, 0.0896)$
CL/F	*Sex*	1.08	8.79	$(0.873, 1.23)$
CL/F	*African American*	1.05	10.9	$(0.806, 1.28)$
CL/F	*Asian*	1.00	8.32	$(0.814, 1.20)$
CL/F	*Hispanic*	1.02	5.87	$(0.871, 1.12)$
CL/F	*Other Race*	0.781	10.2	$(0.620, 0.925)$
CL/F	*CRCL*	0.364	36.3	$(0.202, 0.684)$
CL/F	*Study* 1025	1.17	5.17	$(1.03, 1.29)$
V/F	*Weight*	0.882	7.47	$(0.757, 0.979)$
V/F	*Age*	-0.319	19.4	$(-0.409, -0.177)$

Source: Table 8 on page 35 from study-pmar-00178.pdf

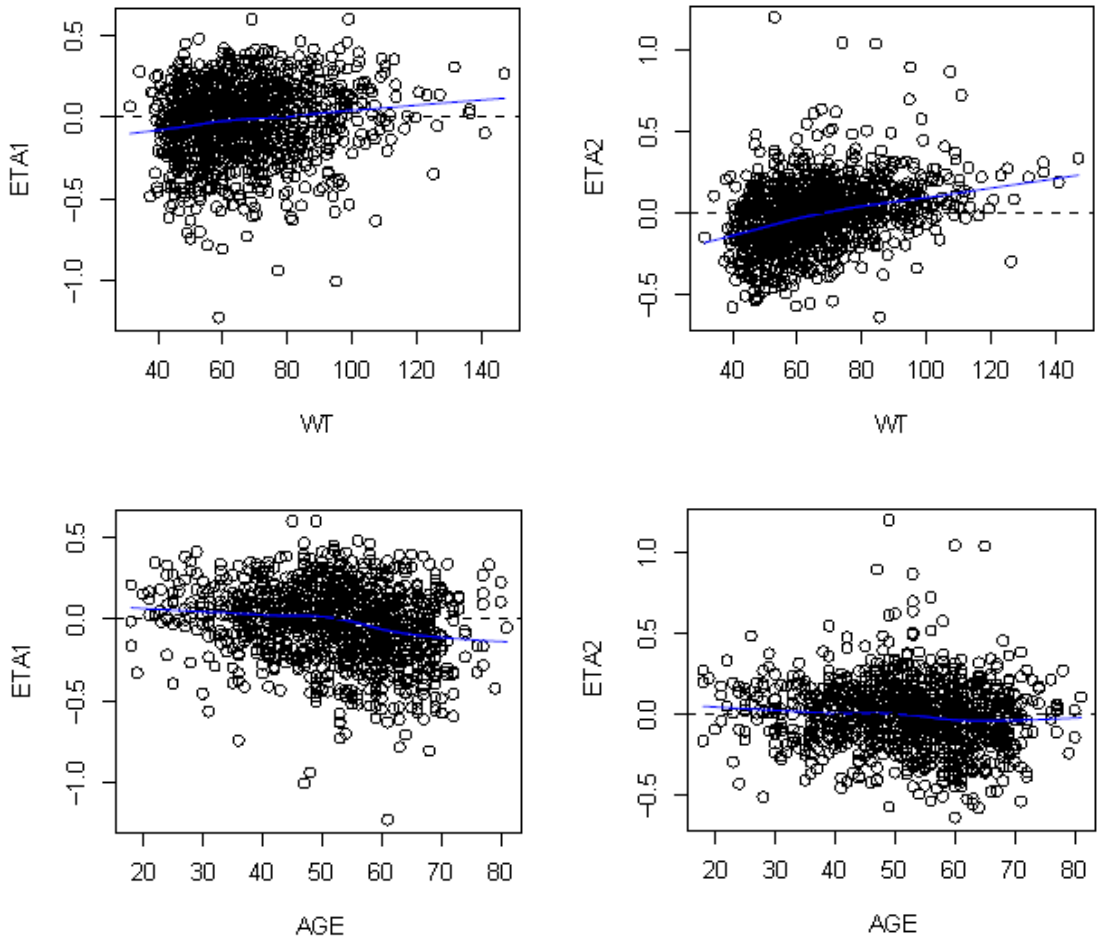


Figure 43: Relationship of variability on CL/F (ETA1) and variability on V/F (ETA2) with weight and age (Base model)

Secondary CP-690,550 exposure metrics (AUC_{ss}, $C_{max,ss}$, $C_{min,ss}$) were calculated using the individual parameter estimates obtained from the final CP-690,550 population PK model.

$$AUC_{ssi} = \frac{DOSE \cdot 1000}{CL_i}$$

$$k_{ei} = \frac{CL_i}{V_i}$$

$$k_{0i} = \frac{DOSE_i}{D1_i}$$

$$C_{max,ssi} = \frac{k_{0i} \cdot 1000}{k_{ei} \cdot V_i} \cdot \frac{1 - exp^{-k_{ei} \cdot D1_i}}{1 - exp^{k_{ei} \cdot \tau}}$$

$$C_{min,ssi} = C_{max,ssi} \cdot exp^{(\tau - D1_i) \cdot k_{ei}}$$

$$C_{ave,ssi} = \frac{AUC_{ssi}}{\tau}$$

where:

- $AUC_{ss,i}$ is the steady-state area under the curve for individual i in ng/mL _ h.
- DOSE is the CP-690,550 dose in mg.
- k_{ei} is the elimination rate constant for individual i in h^{-1}.
- k_{0i} is the calculated dose rate in mg/h.
- $C_{max,ssi}$ is the maximum CP-690,550 concentration at steady-state in ng/mL.
- $C_{min,ssi}$ is the minimum CP-690,550 concentration at steady-state in ng/mL.
- $C_{ave,ssi}$ is the average steady-state CP-690,550 concentration over the 12 hour dosing interval in ng/mL.
- τ is the dosing interval (12 or 24 hours).

Assessment of impact of covariates on AUCss and Cmax,ss metrics

To assess the impact of covariates on AUC_{ss} and $C_{max,ss}$ metrics and to calculate the confidence intervals for each covariate one thousand replicate data sets were simulated using the final model by stratified non-parameteric bootstrap method. The steps involved in this analysis are listed below:

Step 1. Generation of bootstrapped data sets

One thousand replicate data sets were generated by random sampling of the final NONMEM input dataset with replacement, using the individual as the sampling unit, including covariates.

Step 2. Distribution of population parameter estimates

Population parameters for each data set were subsequently estimated using the final model in NONMEM. The confidence intervals were constructed based on 5th and 95th percentiles of those bootstrap runs with successful convergence (827 out of 1000 runs).

Step 3. Calculation of the reference AUC and C_{max} values based on the population estimates

AUC_{ss} and $C_{max,ss}$ for a reference subject were calculated based on the population mean estimates for a typical individual from the model, with reference covariates: 70 kg, 55 years, male, CRCL > 80 mL/min and Caucasian. These calculations are based on the typical $\frac{CL}{F}$ and $\frac{V}{F}$ estimates (18.4 L/h and 96 L, respectively) from the final population PK analysis.

$$AUC_{ss,ref} = \frac{Dose \bullet 1000}{18.4L/h}$$

$$C_{\max,ss,ref} = \frac{k_0 \bullet 1000}{k_e \bullet 96L} \bullet \frac{1-\exp^{-k_e \bullet D1}}{1-\exp^{-k_e \bullet \tau}}$$

where ref=reference subject

Step 4. Calculation of the AUC and C_{max} distributions for different covariates

To calculate the AUC and C_{max} distributions for covariates of interest, first, CL/F and V/F parameters were calculated for each continuous and categorical covariate. These values were then used to calculate the AUC and Cmax parameters for that specific covariate. For example, $\frac{CL}{F}_i$ and $\frac{V}{F}_i$ for a 140 kg subject given the bootstrap results would be:

$$\frac{CL}{F}_{140kg,i} = \frac{CL}{F}_{i} \bullet \left(\frac{140kg}{70kg}\right)^{\theta_{CL,i}}$$

$$\frac{V}{F}_{140kg,i} = \frac{V}{F}_{i} \bullet \left(\frac{140kg}{70kg}\right)^{\theta_{V,i}}$$

These $\frac{CL}{F}_{140kg,i}$ and $\frac{V}{F}_{140kg,i}$ were then used to calculate AUC and C_{max} parameters for that specific covariate.

$$AUC_{ss,\,140kg,\,i} = \frac{Dose \bullet 1000}{\frac{CL}{F}_{140kg,i}}$$

$$C_{max,ss,\,140kg,\,i} = \frac{k_0 \bullet 1000}{k_e \bullet \frac{V}{F}_{140kg,i}} \bullet \frac{1 - \exp^{-ke \bullet D1}}{1 - \exp^{-ke \bullet \tau}}$$

For categorical covariates (e.g. gender), the parameter values were simply calculated using the effect coefficient (θ) as shown below.

$$\frac{CL}{F}_{female,i} = \frac{CL}{F}_{i} \bullet \theta_{CL,i}^{female}$$

$$\frac{V}{F}_{female,i} = \frac{V}{F}_{i} \bullet \theta_{CL,i}^{female}$$

These $\frac{CL}{F}_{female,i}$ and $\frac{V}{F}_{female,i}$ were then used to calculate AUC and C_{max} parameters for that specific covariate.

$$AUC_{ss,\ female} = \frac{Dose \cdot 1000}{\frac{CL}{F}_{female,i}}$$

$$C_{max,ss,} = \frac{k_0 \cdot 1000}{k_e \cdot \frac{V}{F}_{female,i}} \cdot \frac{1 - \exp^{-ke \cdot D1}}{1 - \exp^{-ke \cdot \tau}}$$

Step 5. Calculation of the fold change in AUC_{ss} and $C_{max,ss}$ relative to reference values

Calculate the change in AUC_{ss} and $C_{max,ss}$ parameter values for covariates relative to respective reference values.

For example for a 140 kg subject fold change in AUC and C_{max} with respect to 70 kg reference subject are:

$$\frac{AUC_{ss,140kg,i}}{AUC_{ss,ref}}$$

and

$$\frac{C_{\max,ss,140kg,i}}{C_{\max,ss,ref}}$$

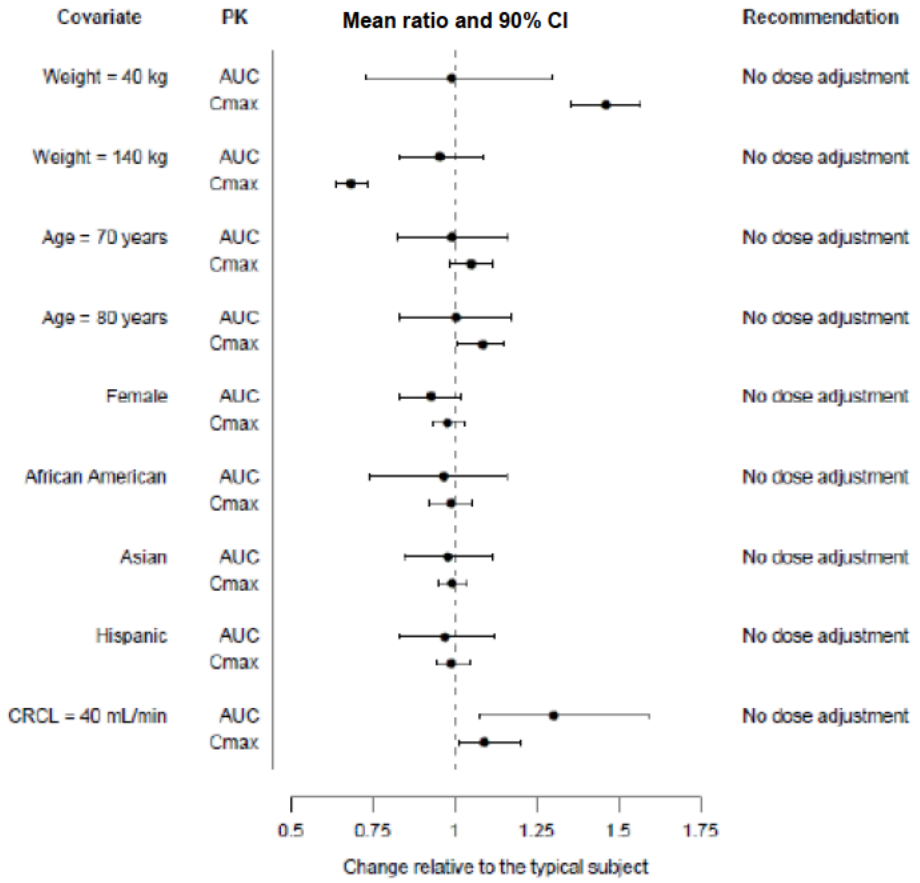
Similarly, fold change in AUC and C_{max} were calculated using $\frac{CL}{F}$ and $\frac{V}{F}$ estimates from all successful convergence runs.

Step 6. Plotting the point estimate and 90% CI for fold change

First, the asymmetric bootstrap confidence intervals were calculated based on ratios obtained from multiple subjects.

The distributions (5th and 95th percentiles) of the nonparametric bootstrap estimates were then plotted as a forest plot where these values were plotted against the reference subject, a 70 kg, 55 years, male, with CRCL > 80 mL/min and Caucasian ethnicity.

The impact of covariates on steady state AUC and Cmax is shown in Figure 44. Also shown are recommendations for dose adjustments.



The typical subject is 70 kg, 55 years old, male, CRCL >= 80 mL/min, and Caucasian

Source: Figure 7 on page 39 from study-pmar-00178.pdf

Figure 44: Impact of Covariates on the Pharmacokinetics of CP-690,550

Conclusions

The population PK of CP-690,550 in patients with RA was described by a one-compartment model with zero order absorption.

CP-690,550 CL/F is not time-dependent in patients with RA.

CP-690,550 CL/F or Cave was unaffected over the range of body weights and ages studied as well as race and gender.

Patients with lower body weights are expected to have higher $C_{max,ss}$ and lower $C_{min,ss}$ compared to those with higher body weights.

The relationship between CP-690,550 CL/F and CRCL is consistent with the known contribution of renal excretion to the clearance of CP-690,550.

Variability in CP-690,550 PK was relatively low, with final estimates of unexplained variability in CL/F and V/F of 26.6 CV% and 26.0 CV%, respectively.

Reviewer's Comment: *The population pharmacokinetic analysis conducted by the sponsor is acceptable. The pharmacokinetic model submitted by the sponsor was run using NONMEM® (Ver 7.1.2) to confirm labeling statements. The proposed labeling statements regarding intrinsic factors are acceptable. However, note that conclusion* (b) (4) *was true after accounting for differences in renal function or CRCL between patients.*

4. REVIEWER'S ANALYSIS

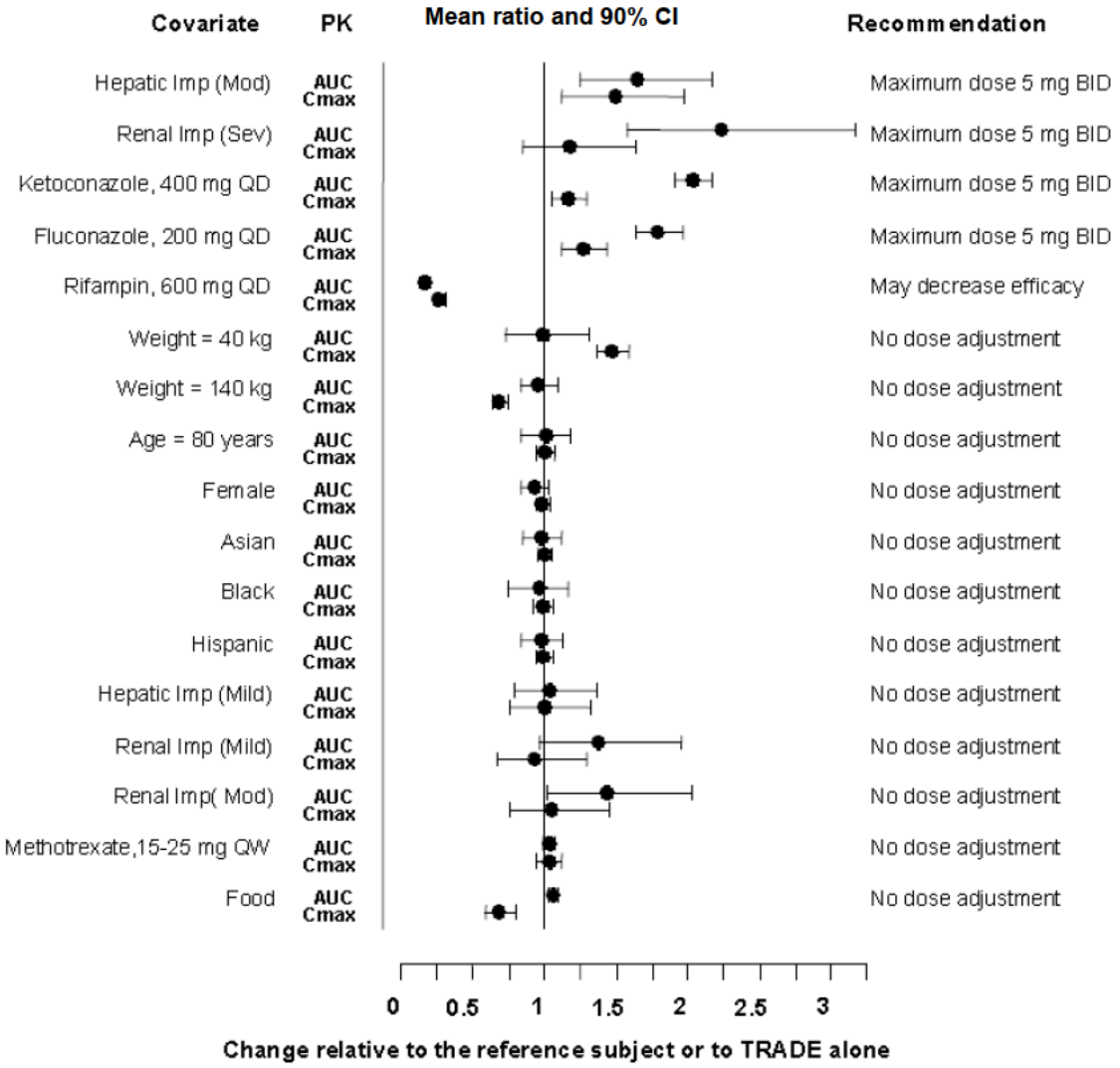
4.1. Introduction

Sponsor proposed labeling statements regarding influence of age, gender, weight, race and CRCL on tofacitinib pharmacokinetics using nonlinear mixed effects analysis.

4.2. Objectives

Analysis objectives were:

- To confirm sponsor's proposed labeling statements regarding age, gender, weight, race and CRCL effects
- To confirm sponsor's labeling with respect to PK data and dosing recommendations for the above mentioned covariates (as shown in Figure 45)



Reference values for weight, age, gender, and race comparisons are 70 kg, 55 years, male, and White, respectively; reference groups for renal and hepatic impairment data are subjects with normal renal or hepatic function, respectively; and reference group for drug interaction and food effect studies is administration of TRADE alone; Mod=moderate; Sev=severe; Imp=impairment

Figure 45: Dosing recommendations based on pharmacokinetic data (reproduced from the sponsor proposed label)

4.3. Methods

4.3.1. Data Sets

Data sets used are summarized in Table 32.

Table 32. Analysis Data Sets

Study Number	Name	Link to EDR
PMAR-00178	Population Pharmacokinetics of CP-690,550 in Patients with Rheumatoid Arthritis	\\Cdsesub1\EVSPROD\NDA203214\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pmar-00178

4.3.2. Software

NONMEM (Ver 7.1.2)

4.3.3. Models

Sponsor's PK model with inter-individual and inter-occasion variability was used for analysis. Impact of covariates on AUC and Cmax metrics was assessed based on bootstrap outputs using the steps outlined under heading "**assessment of impact of covariates on AUCss and Cmax,ss metrics"** in section 3 (Results of Sponsor's Analysis). This analysis was performed in SAS and the code used is included in appendix 1.

4.4. Results

The results from reviewer's analysis are similar to sponsor's analysis.

Reviewer's analysis findings:

Weight

Population PK analysis in rheumatoid arthritis patients indicated that systemic exposure (AUC) of TRADE in the extremes of body weight (40 kg, 140 kg) were similar to that of a 70 kg patient after accounting for differences in CRCL. The geometric mean ratio and 90% CI for comparison of AUC_{ss} and $C_{max,ss}$ based on weight are shown in Table 33, with less than 5% difference in AUC for patients with body weight of 40 kg and 140 kg relative to the mean weight of 70 kg.

An approximately linear relationship between body weight and volume of distribution was observed (Figure 43), which would result in higher peak (C_{max}) and lower trough (C_{min}) concentrations in lighter patients. Mean C_{max} for a 40 kg patient was 46% higher and for a 140 kg patient 31% lower than that of a 70 kg patient. However, these differences in Cmax were not considered important, given that 10 mg BID and 20 mg QD had similar efficacy in study A3921025. With respect to safety, safety profile for double the dose (i.e., 10 mg dose) with approximately 100% higher C_{max} is known.

Age

Elderly patients age 70 years and 80 years were estimated to have <10% difference in AUC and Cmax relative to the mean age of 55 years after accounting for differences in CRCL. The geometric mean ratio and 90% CI for comparison of AUC_{ss} and $C_{max,ss}$ based on age are shown in Table 33.

Gender

Women were estimated to have 7% lower mean AUC and 2% lower mean C_{max} compared to men after accounting for differences in CRCL. The geometric mean ratio and 90% CI for comparison of AUC_{ss} and $C_{max,ss}$ based on gender are shown in Table 33.

Race

The available data have also shown that there are no major differences in tofacitinib AUC and C_{max} between White, Black and Asian patients after accounting for differences in CRCL. The geometric mean ratio and 90% CI for comparison of AUC_{ss} and $C_{max,ss}$ based on race are shown in Table 33.

Variability estimate for AUC

Interindividual variability (% CV) estimates from the final model was 26.6% for CL/F which would result in approximately 27% variability in AUC of tofacitinib.

Table 33: Assessment of impact of covariates on AUCss and Cmax,ss based on output from bootstrap analysis

Covariate comparison (Test vs. Reference)	AUCss		Cmax,ss	
	GMR	90%CI	GMR	90% CI
Weight 140 kg vs. 70 kg	0.97	0.83-1.09	0.69	0.64-0.74
Weight 40 kg vs. 70 kg	1.01	0.73-1.30	1.46	1.36-1.57
Age 70 years vs. 55 years	0.99	0.83-1.16	1.05	0.98-1.11

Age 80 years vs. 55 years	1.00	0.83-1.18	1.08	1.01-1.15
Female vs. Male	0.93	0.83-1.02	0.98	0.93-1.03
African American vs. White	0.96	0.74-1.16	0.99	0.92-1.05
Asian vs. White	0.98	0.85-1.12	0.99	0.95-1.04
Hispanic vs. White	0.97	0.83-1.12	0.99	0.95-1.05
CRCL 40 mL/min vs. 80 mL/min	1.32	1.08-1.59	1.10	1.01-1.20

Sponsor's analysis findings

Population PK analysis in rheumatoid arthritis patients indicated that systemic exposure (AUC) of TRADE in the extremes of body weight (40 kg, 140 kg) were similar to that of a 70 kg patient. Elderly patients 80 years of age were estimated to have less than 5% higher AUC relative to the mean age of 55 years. Women were estimated to have 7% lower AUC compared to men. The available data have also shown that there are no major differences (<5%) in TRADE AUC between White, Black and Asian patients. An approximately linear relationship between body weight and volume of distribution was observed, resulting in higher peak (C_{max}) and lower trough (C_{min}) concentrations in lighter patients. However, this difference is not considered to be clinically relevant. The between-subject variability (% coefficient of variation) in AUC of TRADE is estimated to be approximately 27%.

Reviewer's comment

The labeling statement, as proposed by sponsor, regarding age, weight, gender and race effects on tofacitinib pharmacokinetics are acceptable

LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
502mod.ctl tasocomb.csv	PK model and data set used by reviewer	P:\Reviews\Ongoing PM Reviews\Tofacitinib_NDA203214_VAB\PPK Analyses\Final Model
502mod.lst	Output file	P:\Reviews\Ongoing PM Reviews\Tofacitinib_NDA203214_VAB\PPK Analyses\Final Model\502mod nm7

Appendix 1

```
/* SAS Code to calculate the fold change in AUC and Cmax based on
output from Bootstrap Analysis for Tofacitinib*/
```

(b) (4)

[redacted]

5 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	203214
Submission Date	10/21/2011
Applicant Name	Pfizer
Generic Name	Tofacitinib
Proposed Indication	Rheumatoid Arthritis
Primary Reviewer	Jeffrey Kraft, PhD
Secondary Reviewer	Mike Pacanowski, PharmD, MPH

1 Background

The current submission is for tofacitinib, a potent inhibitor of JAK kinases, to be indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs. Tofacitinib is cleared mainly via hepatic metabolism (~70%) by CYP3A4 (primary) and CYP2C19 (secondary). The sponsor submitted summary results from a study in healthy subjects (A3921028) in which the impact of CYP2C19 genetic variation on tofacitinib exposure and clearance was investigated. The purpose of this review is to determine genetic variation within CYP2C19 have a clinically relevant impact on tofacitinib clearance.

2 Submission Contents Related to Genomics

2.1 Contents

The sponsor submitted summary level data for CYP2C19 genotyping performed in a healthy volunteer study (A3921028; n=60) in order to investigate the effect of CYP2C19 variation on the exposure and clearance of tofacitinib. Subject-level genotype data were not included in the current submission. No labeling claims related to CYP2C19 genotype have been proposed.

Comment: DNA was collected in Phase 2/3 clinical trials on a voluntary basis allowing for additional pharmacogenetic studies if indicated on the basis of tofacitinib's efficacy and safety.

2.2 Methods

CYP2C19 genotype and pharmacokinetic data were available from 60 healthy subjects who received a single 100 mg dose of tofacitinib as part of a QT study. Samples were processed and analyzed by Pfizer. The sponsor genotyped for the *2, *3, *4, *5, and *17 alleles of the CYP2C19 gene. The sponsor classified each subject's metabolizer status based on genotype as follows: poor metabolizers (PMs) – *2/*2, *2/*3, or *3/*3 alleles; ultra-rapid metabolizers (UMs) – *17/*17; or extensive metabolizers (EMs) – all other

allele combinations.

Comment: The sponsor genotyped the most frequent alleles to determine metabolizer status for CYP2C19. The approach for determining metabolizer status is reasonable. However, null allele heterozygotes were not classified intermediate metabolizers, thus results may be biased toward the null. Analytical methods for genotyping were not described.

3 Key Questions and Summary of Findings

3.1 Does genetic variation in CYP2C19 influence tofacitinib exposure of clearance?

The sponsor's analysis indicates that the mean AUC and Cmax were approximately 15% higher for PMs (N=6) compared to EMs (N=52). This suggests that genetic variation with CYP2C19 does not significantly influence tofacitinib exposure.

Table 10. Summary of Plasma CP-690,550 Pharmacokinetic Parameter Values

	Summary Statistics[a] by Genotype			
Parameter, units	All Subjects (N=60)	Extensive Metabolizers (N=52)	Poor Metabolizers (N=6)	Individual Values[b] for Ultra Extensive Metabolizers (N=2)
AUClast, ng.hr/mL	2670 (28)	2670 (28)	3114 (12)	2180, 1280
AUCinf, ng.hr/mL	2683 (28)	2683 (28)	3130 (12)	2190, 1290
Cmax, ng/mL	564 (34)	565 (31)	647 (41)	530, 227
Tmax, hr	1.0 (0.3-4.1)	1.0 (0.3-4.1)	0.5 (0.3-4.0)	2.0, 2.0
t½, hr	3.28 (15)	3.32 (15)	3.01 (12)	3.33, 3.07

Source: Tables 13.5.2 and 13.5.2.1 Appendix B5.2.2.1
[a]Geometric mean (%CV) for AUC and C_{max}; median (range) for T_{max}; arithmetic mean (%CV) for t½.
[b]Parameter values for Subjects 10021042 and 10021043, respectively.

Comment: The sponsor's analysis is based on relatively low numbers of PMs (N=6). Given the summary level data provided, conclusions about the lack of impact of CYP2C19 on tofacitinib exposure or clearance seem reasonable. The prevalence of poor metabolism appears high in this study compared to U.S. white and black populations (10% vs. 3-5%), thus the results should be interpreted with caution.

A significant dose- and exposure-response relationship was observed for efficacy (e.g., ACR20) and safety (e.g., anemia; see Pharmacometrics review). However, tofacitinib exposure is not significantly affected by race, and exposures are not highly variable (see OCP Question-Based Review).

Comment: Lack of race effects or significant variability lessens the likelihood of a significant genetic contribution to tofacitinib PK.

4 Summary and Conclusions

Dose and plasma concentrations are associated with clinical response (see Pharmacometrics review). The in-vitro and mass-balance suggest that tofacitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C19.

The sponsor recommends dose adjustment for patients receiving drug(s) that inhibit both CYP3A4 and CYP2C19 (e.g., fluconazole) because of an approximate two-fold increase in exposure. However, tofacitinib dose adjustment is not warranted when coadministered with a CYP2C19 inhibitor.

The pharmacogenetic analysis conducted by the sponsor suggests that CYP2C19 metabolic status has little effect on tofacitinib PK. Therefore, dosing recommendations based on genotype alone do not appear to be indicated.

Dose adjustment may be indicated in patients who CYP2C19 poor metabolizers also receiving a CYP3A4 inhibitor given that the exposure level expected in this scenario is similar to that observed with fluconazole.

5 Recommendation

The submitted data suggest a limited role of CYP2C19 genotype on the pharmacokinetics of tofacitinib. No additional action is indicated.

5.1 Post marketing studies

None.

5.2 Labeling

None.

INDIVIDUAL STUDY REVIEW

NDA	203214
Submission Date	10/21/2011
Brand Name	TBD
Generic Name	Tofacitinib
Clinical Pharmacology Reviewer	Lokesh Jain, Ph.D.
Pharmacometrics Reviewer	Lokesh Jain, Ph.D. and Atul Bhattaram, Ph.D.
Pharmacogenomics Reviewer	Jeffrey Kraft, Ph.D.
Pharmacometrics Team Leader	Atul Bhattaram, Ph.D.
Pharmacogenomics Team Leader	Michael Pacanowski, Pharm.D., M.P.H.
Clinical Pharmacology Team Leader	Suresh Doddapaneni, 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)	Tablet ; 5 mg and 10 mg
Indication	Rheumatoid Arthritis
Dosage Regimen	5 mg BID; some patients may benefit from an increase to 10 mg BID based on clinical response

Note –

In this review, early development names (b) (4) and CP-690,550 are also used to refer to tofacitinib

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ADME In-Vitro STUDIES

Absorption and Transporters

Study # XT088024 [redacted] (b) (4)

Title: in vitro studies in MDCK-MDR1 cells to identify compound [redacted] (b) (4) as substrate for p-glycoprotein

- **Objective:** To investigate whether [redacted] (b) (4) is a human P-glycoprotein (P-gp) substrate
- **Method:** Bidirectional transport of the [redacted] (b) (4) (3, 12 and 102 μM) was determined through parental and MDR1 transfected MDCKII cell monolayers. Digoxin efflux ratio was assayed as a positive control for MDR1 mediated transport. The bidirectional transport of [redacted] (b) (4) on parental and MDR1 transfected MDCKII cells was also determined in the presence and absence of P-gp inhibitors ketoconazole and verapamil
- **Results:** The bidirectional transport of [redacted] (b) (4) through control MDCKII cells and MDR transfected MDCKII-MDR1 monolayers in time is shown in Figure 46. The ratio of [redacted] (b) (4) efflux in MDCKII-MDR1 cells and MDCKII parental cells is shown in Table 34, which was approximately 11-12. Efflux of [redacted] (b) (4) tested at 12 μM concentration, was abolished in the presence of either ketoconazole or verapamil (Table 35).

Table 34: Ratio of [redacted] (b) (4) efflux in MDCKII-MDR1 cells and MDCKII parental cells

Concentration [redacted] (b) (4) (μM)	Efflux ratio MDCKII-MDR1 cells (± SD)	Efflux ratio MDCKII parental cells (± SD)	ER_{MDR1}/ER_{MDCKII} (± SD)
3	18.43 (± 0.08)	1.64 (± 0.11)	11.22 (± 0.07)
12	21.17 (± 0.21)	1.85 (± 0.29)	11.44 (± 0.16)
102	10.43 (± 0.05)	0.87 (± 0.12)	11.97 (± 0.14)

Table 35: Inhibition of efflux of [redacted] (b) (4) (12 μM) by the P-glycoprotein inhibitors ketoconazole (50 μM) and verapamil (100 μM) in MDCKII-MDR1 cells

Inhibitor	Mean A-B P_{app} ($x10^{-6}$cm/s) (n=3)(±SD)	Mean B-A P_{app} ($x10^{-6}$cm/s) (n=3)(±SD)	ER (± SD)	Mean A-B Recovery (percent) (n=3)(±SD)	Mean B-A Recovery (percent) (n=3)(±SD)
Ketoconazole	8.88 (± 1.14)	8.61 (± 2.01)	0.97 (± 0.21)	97 (± 3)	97 (± 6)
Verapamil	5.21 (± 1.09)	7.64 (± 0.83)	1.50 (± 0.23)	105 (± 11)	98 (± 4)

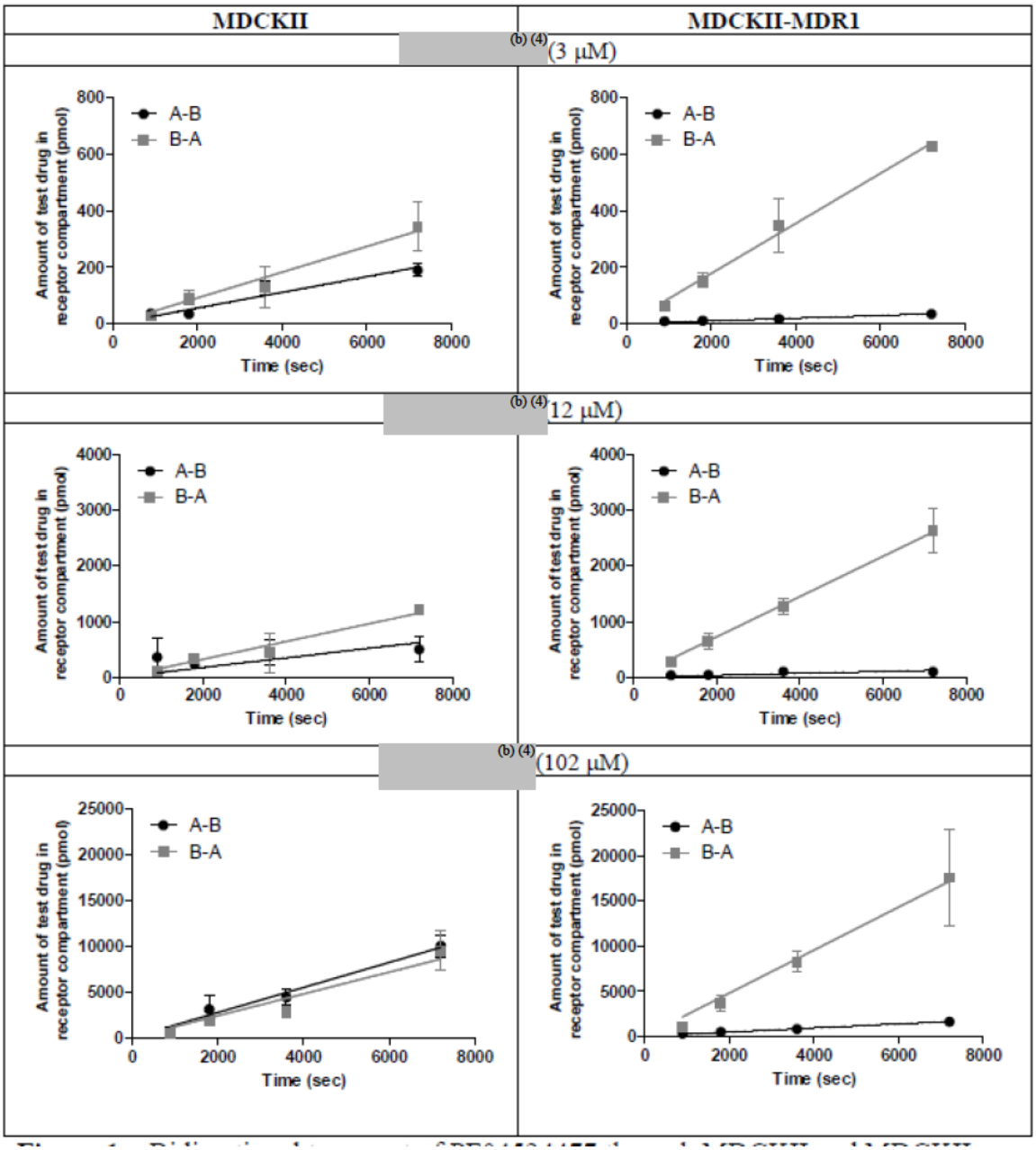

Figure 46: Bidirectional transport of (b) (4) through MDCKII and MDCKII-MDR1 monolayers in time

- **Conclusions:** High efflux in MDCKII-MDR1 cells compared to the parental cell line and abolition of this efflux in the presence of known P-gp inhibitors in MDCKII-MDR1 cells shows that (b) (4) is a substrate of human P-glycoprotein.

Study # 060532

Title: The in vitro study of P-glycoprotein inhibition by [redacted] (b) (4) (CP-690550) in CACO-2 cells

- **Objective:** To investigate whether [redacted] (b) (4) inhibits the transport of [^{3}H]-Digoxin in Caco-2 cells.
- **Method:** In vitro apical-to-basal (a-b) and basal-to-apical (b-a) permeability for digoxin was assessed across monolayers of the human colon carcinoma derived cell line Caco-2 with and without [redacted] (b) (4)
- **Results:** [redacted] (b) (4) is a low potency inhibitor of digoxin flux in Caco-2 cells, with 72% inhibition at maximum concentration of 1000 µM. The estimated IC_{50} for [redacted] (b) (4) [redacted] (b) (4) against the degree of activity of digoxin flux is 311 µM (Figure 47).

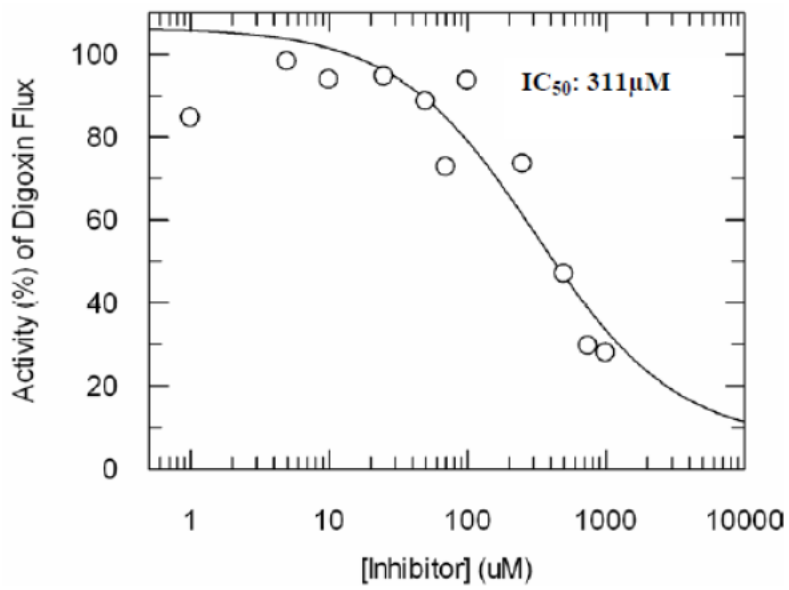

Figure 47: Degree of activity of digoxin flux across Caco-2 cell monolayers in the presence of increasing amounts of [redacted] (b) (4)

- **Conclusion:** Peak plasma concentration following 10 mg bid multiple-dose administration was approximately 310 nM or 0.310 µM, suggesting that at clinically relevant concentration [redacted] (b) (4) will have low potential for P-gp inhibition.

Study # 175813

Title: CP-690550: BCRP substrate evaluation

- **Objective:** To determine whether CP-690550 was a substrate of the efflux transporter, BCRP (breast cancer resistance protein)
- **Method:** Apical to basolateral (AB) and basolateral to apical (BA) permeability were measured in order to determine the efflux ratio (BA Papp/AB Papp) of CP-690550 by itself and in the presence of Ko143 (known BCRP inhibitor), in MDCK cells

transfected with BCRP. Topotecan (BCRP substrate) was evaluated as positive control.

- **Results and Conclusions:** CP-690550 is not a substrate of BCRP efflux. In the presence and absence of Ko143, the efflux ratios for CP-690550 remained below the cutoff of 2.5 (Table 36). The positive control topotecan had an efflux ratio of 5.8, and in the presence of Ko143 the efflux ratio lowered to unity

Table 36: Permeability and Efflux Ratio Results

Compound(s)	P_{app} Avg. (AB)	P_{app} Avg. (BA)	Efflux Ratio
CP-690550 – 2 µM	13.5	12.7	0.94
CP-690550 – 2 µM + Ko143	12.9	13.1	1.02
CP-690550 – 20 µM	12.7	13.4	1.05
CP-690550 – 20 µM + Ko143	13.8	14.0	1.01
Topotecan – 2 µM	1.28	7.44	5.83
Topotecan – 2 µM + Ko143	3.64	3.38	0.93

Additional Information:

* P_{app} = x10^{-6} cm/sec
* Efflux Ratio = BA average P_{app} / AB average P_{app}, Efflux Ratio > 2.5 = substrate for BCRP efflux
* Ko143 – BCRP inhibitor marker, tested at 10 µM
* Topotecan – BCRP substrate marker

Study # 192119

Title: In vitro inhibition of OATP 1B1 by CP-690550

- **Objective:** To determine the inhibitory potency of CP-690550 against the human hepatic uptake transporter OATP 1B1 when expressed in HEK293 cells. The uptake of pravastatin was used as the probe substrate
- **Method:** The inhibition of human OATP 1B1 by CP-690550 was assessed using HEK293 cells over-expressing recombinant human OATP 1B1
- **Results:** The results show a concentration-dependent inhibition of human OATP 1B1 by CP-690550 (Table 37). The IC50 for CP-690550 against OATP 1B1 was estimated at 55.3 µM (Figure 48).
- **Conclusion:** *In vitro*, CP-690550 appears to be an inhibitor of human OATP 1B1. However, at peak plasma concentration for 10 mg bid dose, CP-690550 has low potential for inhibition for OATP 1B1.

Table 37: The Effect of CP-690550 on the Uptake of Pravastatin by OATP 1B1

Concentration of CP-690550 (μM)	Pravastatin Uptake by HEK-OATP 1B1 (peak area/mg protein/min x10^5)	Degree of Inhibition (%)
0	35.60 ± 3.25	-
0.1	29.82 ± 0.19	16.4
10	28.11 ± 1.72	21.3
31.25	19.97 ± 1.19	44.4
62.5	14.75 ± 0.80	59.2
125	11.60 ± 0.45	68.2
250	7.81 ± 0.38	79.0
375	7.79 ± 0.10	79.0
500	5.53 ± 0.17	85.4
750	4.31 ± 0.15	88.9
1000	2.50 ± 0.81	94.0
Rifamycin SV (30 μM)	0.40 ± 0.05	100.0

Data are mean ± SD of triplicate measurements

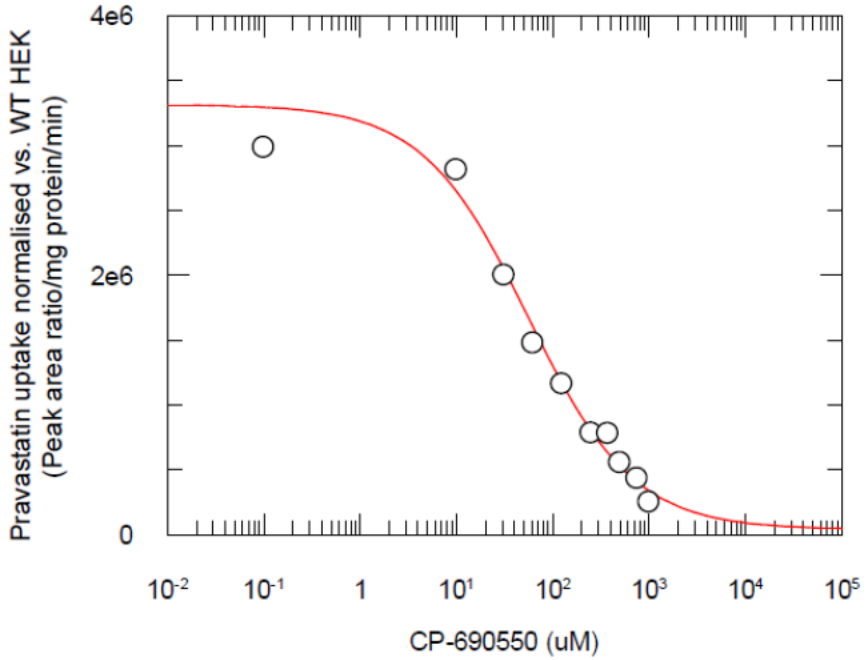

Figure 48: Inhibition of Pravastatin Uptake by CP-690550

Study # 095440

Title: In vitro inhibition of OATP 1B3 by CP-690550

- **Objective:** To determine the inhibitory potency of CP-690550 against the human hepatic uptake transporter OATP 1B3 when expressed in HEK293 cells. The uptake of rosuvastatin was used as the probe substrate
- **Method:** The inhibition of human OATP 1B3 by CP-690550 was assessed using HEK293 cells expressing recombinant human OATP 1B3
- **Results and Conclusion:** No inhibition of human OATP 1B3 by CP-690550 was observed up to tested concentrations of 100 μM (Figure 49).

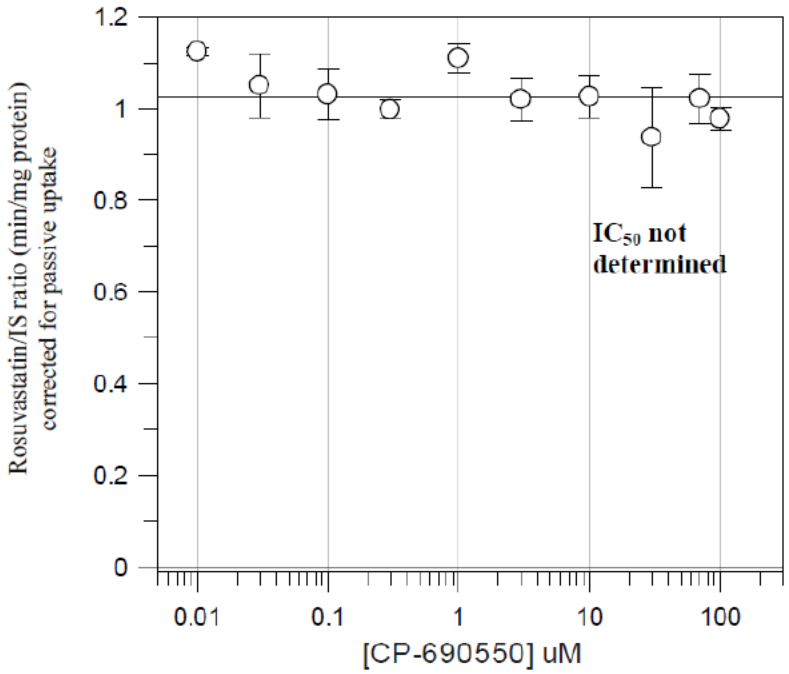

Figure 49: Inhibition of Rosuvastatin Uptake by HEK-OATP 1B3 Cells by CP-690550

Study # 135323

Title: *In Vitro* Renal Transport Inhibition by CP-690,550

- **Objective:** To investigate the potential of CP-690,550 to inhibit the human OCT2 mediated uptake of Creatinine.
- **Method:** The inhibition of human OCT2 by CP-690550 was assessed using Human Embryonic Kidney (HEK 293) cells transfected with human OCT2
- **Results:** In the concentration range tested (1 µM-4.1 mM), CP-690,550 inhibited the uptake of Creatinine mediated by hOCT2 in a dose-dependent manner. CP-690,550 and two positive controls, Cimetidine and Quinidine, were all able to inhibit hOCT2-mediated uptake of Creatinine (Figure 50).
- **Conclusion:** The IC_{50} for inhibition of hOCT2 by CP-690,550 was 150 µM. At clinically relevant concentrations of approximately 310 nM (i.e., peak plasma concentrations at 10 mg bid), CP-690,550 has low potential to inhibit hOCT2.

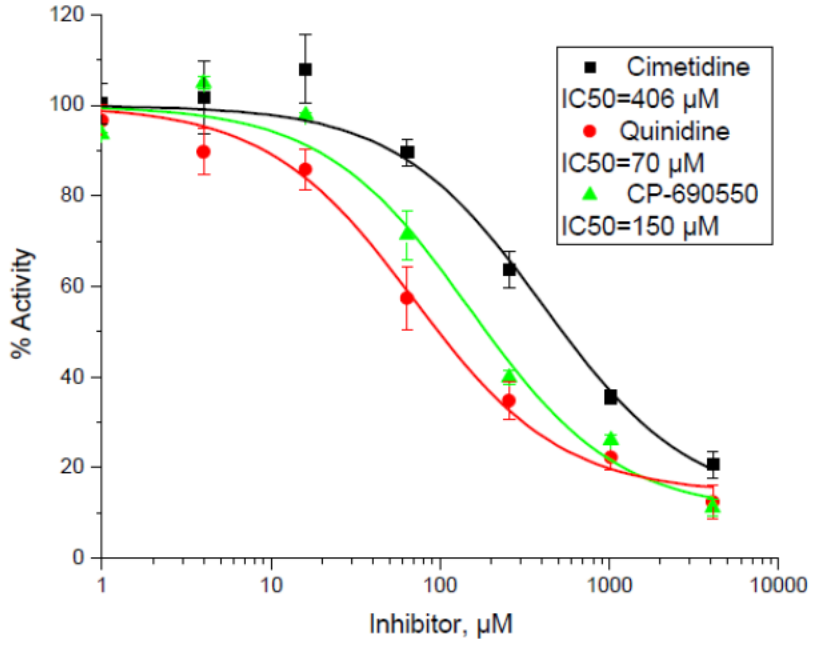

Figure 50: CP-690,550 inhibition of 5 µM Creatinine uptake mediated by hOCT2. Cimetidine and Quinidine were used as positive controls. The estimated IC50s for CP-690,550, Cimetidine and Quinidine were 150 µM, 406 µM and 70 µM, respectively

Distribution

Study # DM2001-690550-018

Title: Plasma Protein Binding of CP-690,550 in Mouse, Rat, Dog, Monkey and Human

- **Objective:** To determine the degree of plasma protein binding of CP-690,550 in mouse, rat, dog, monkey and human
- **Method:** Pooled plasma from mouse, rat, dog and monkey and human plasma segregated by individuals were used to determine the extent of protein binding by ultrafiltration. The samples were analyzed using LC/MS/MS
- **Results and Conclusion:** CP-690,550 shows moderate plasma protein binding for mouse, rat, dog, monkey and human (Table 38).

Table 38: Summary of plasma protein binding in mouse, rat, dog, monkey and human

Species	Nominal Concentration (ng/ml)	Fu (%)	Fu
Mouse	156	60.7 ± 0.5	0.607 ± 0.005
Rat	156	69.1 ± 0.6	0.691 ± 0.006
Dog	156	81.1 ± 4.9	0.811 ± 0.049
Monkey	156	74.8 ± 0.0	0.748 ± 0.000
Human	156	57.9 ± 2.23	0.579 ± 0.022
Mouse	1250	69.0 ± 0.8	0.690 ± 0.008
Rat	1250	91.3 ± 0.5	0.913 ± 0.005
Dog	1250	76.4 ± 12.5	0.764 ± 0.125
Monkey	1250	56.0 ± 6.6	0.560 ± 0.066
Human	1250	63.2 ± 2.44	0.632 ± 0.024
Mouse	2500	71.9 ± 2.9	0.719 ± 0.029
Rat	2500	93.7 ± 4.2	0.937 ± 0.042
Dog	2500	82.3 ± 7.0	0.823 ± 0.070
Monkey	2500	63.5 ± 1.6	0.635 ± 0.016
Human	2500	63.3 ± 5.33	0.633 ± 0.053

Mouse, Rat, Dog and Monkey data are based on pooled samples. Human data are reported as mean of 5 individuals

Study # DM2002-690550-025

Title: Protein Binding of CP-690,550 in Human Serum Albumin and α1-Acid Glycoprotein

- **Objective:** To determine the degree of protein binding of CP-690,550 in human serum albumin (HSA) and α1-acid glycoprotein (AAG)
- **Method:** Protein binding was determined using freshly prepared matrix of HSA at 40 mg/mL or AAG at 0.75 mg/mL using ultrafiltration method.
- **Results and Conclusion:** CP-690,550 does not appear to bind to AAG as the mean fraction unbound was approximately 1.2 at concentrations of 156 ng/mL, 1250 ng/mL and 2500 ng/mL (Table 39). At these concentrations, mean fraction unbound for HSA was approximately 0.5 (Table 39), indicating moderate binding to HSA independent of initial concentrations. Fraction unbound to HSA (i.e., ~0.5) was close to the unbound fraction observed for total plasma protein in study DM2001-690550-018 (i.e., ~0.58-0.63), suggesting CP-690,550 predominantly binds to HSA.

Table 39: CP-690,550 Protein Binding at 156, 1250 and 2500ng/mL to (A) AAG and (B) HSA

A. AAG

Nominal Incubation [ ] (ng/mL)	Initial Incubate [ ] (ng/mL)	Ultrafiltrate [ ] (ng/mL)	Fraction Unbound
156	96.1	102	1.01
156	112	116	1.15
156	99.5	125	1.24
156	88.9	125	1.24
156	109	134	1.33
Mean	**101**	-----	**1.19**
SD	**9.46**	-----	**0.12**
1250	968	1150	1.17
1250	958	1110	1.13
1250	947	975	1.00
1250	933	1150	1.17
1250	1090	999	1.02
Mean	**979**	----	**1.10**
SD	**63.3**	----	**0.08**
2500	1630	2050	1.22
2500	1770	2100	1.25
2500	1540	2360	1.40
2500	1850	1880	1.12
2500	1590	1690	1.01
Mean	**1680**	----	**1.20**
SD	**130**	----	**0.15**

B. HSA

Nominal Incubation [ ] (ng/mL)	Initial Incubate [ ] (ng/mL)	Ultrafiltrate [ ] (ng/mL)	Fraction Unbound
156	156	80.0	0.55
156	141	73.7	0.51
156	138	71.8	0.50
156	143	73.7	0.51
156	147	73.2	0.50
Mean	**145**	----	**0.51**
SD	**6.96**	----	**0.02**
1250	1160	598	0.50
1250	1200	636	0.53
1250	1190	613	0.51
1250	1220	665	0.55
1250	1230	621	0.52
Mean	**1200**	----	**0.52**
SD	**27.4**	----	**0.02**
2500	2520	1220	0.49
2500	2570	1180	0.47
2500	2380	1160	0.47
2500	2450	1260	0.51
2500	2530	1290	0.52
Mean	**2490**	----	**0.49**
SD	**75.2**	----	**0.02**

Study # 055956

Title: Blood to plasma concentration ratio of CP-690550 in rat, monkey and human whole blood

- **Objective:** To determine the blood to plasma concentration ratio of CP-690550 at a concentration of 1 µM (equivalent to 0.312 µg/mL) in rat, monkey and human blood from pooled gender sources
- **Method:** CP-690550 was added to pooled whole blood samples from different species to the concentrations of 1 µM. Aliquotes were drawn at 60 and 300 minutes to analyze the CP-690550 concentrations in whole blood and plasma.
- **Results and Conclusion:** The mean blood to plasma concentration ratios of CP-690550 were approximately 1.2 in all three species at 1 µM. This suggests approximately similar distribution of CP-690550 in blood and plasma.

In vitro Metabolism

Study # DM2004-690550-046

Title: Identification of *In Vitro* Metabolites of CP-690,550 in Human Liver Microsomes and Recombinant Cytochrome P-450 isoforms

- **Objective:** To identify *in vitro* metabolites of CP-690,550 in human liver microsomes and recombinant CYP 450 isoforms
- **Method:** Radiolabeled drug was incubated with liver microsomes and recombinant CYPs and quantitation of metabolites was carried out by measuring the radioactivity.
- **Results and Conclusion:** In incubations with human liver microsomes a total of 10 metabolites were detected along with parent. The relative percentages of metabolites were identified with recombinant CYPs. As shown in Table 40, turnover of CP-690,550 was highest in CYP3A4 (83.6%), followed by 2C19 (44%), 3A5 (16%), 1A2 (9.5%) and 2D6 (8.8%). No turnover was found in the CYP2C9, 2E1 and 2C8 intubations. The proposed metabolic pathway of CP-690,550 is shown in Figure 51.

Table 40: Percentage of Metabolites of CP-690,550 in Human Liver Microsomes and Recombinant Human Cytochrome P-450 Isoforms

Metabolite	m/z	RT(min)	Human Microsome	3A4	2C19	2D6	1A2	3A5
M14	345	9.1	3.4	5.4				
M15	329	10.0	1.5	5.3			1.3	1.4
M25	347	12.5	2.1	6.8	3.0			0.5
M18	329	13.0	2.2	6.2				0.7
M5	320	16.2	9.0	20.4				3.0
M1	299	16.8	2.4					
M2	304	17.2	5.7	6.1*				1.7*
M3	336	19.3		5.1				
CP-690,550	313	20.4	59.2	16.4	56.1	91.2	90.5	84.1
M8	329	23.8	3.4	9.6	3.9	1.7		1.4
M9	329	26.7	4.0	5.0	34.2	7.2	2.7	1.9
M22	343	30.9	2.1	2.6	1.0			
Unknown		33.6	1.7	3.7	1.8		5.5	5.2

* Mixture of M1 and M2

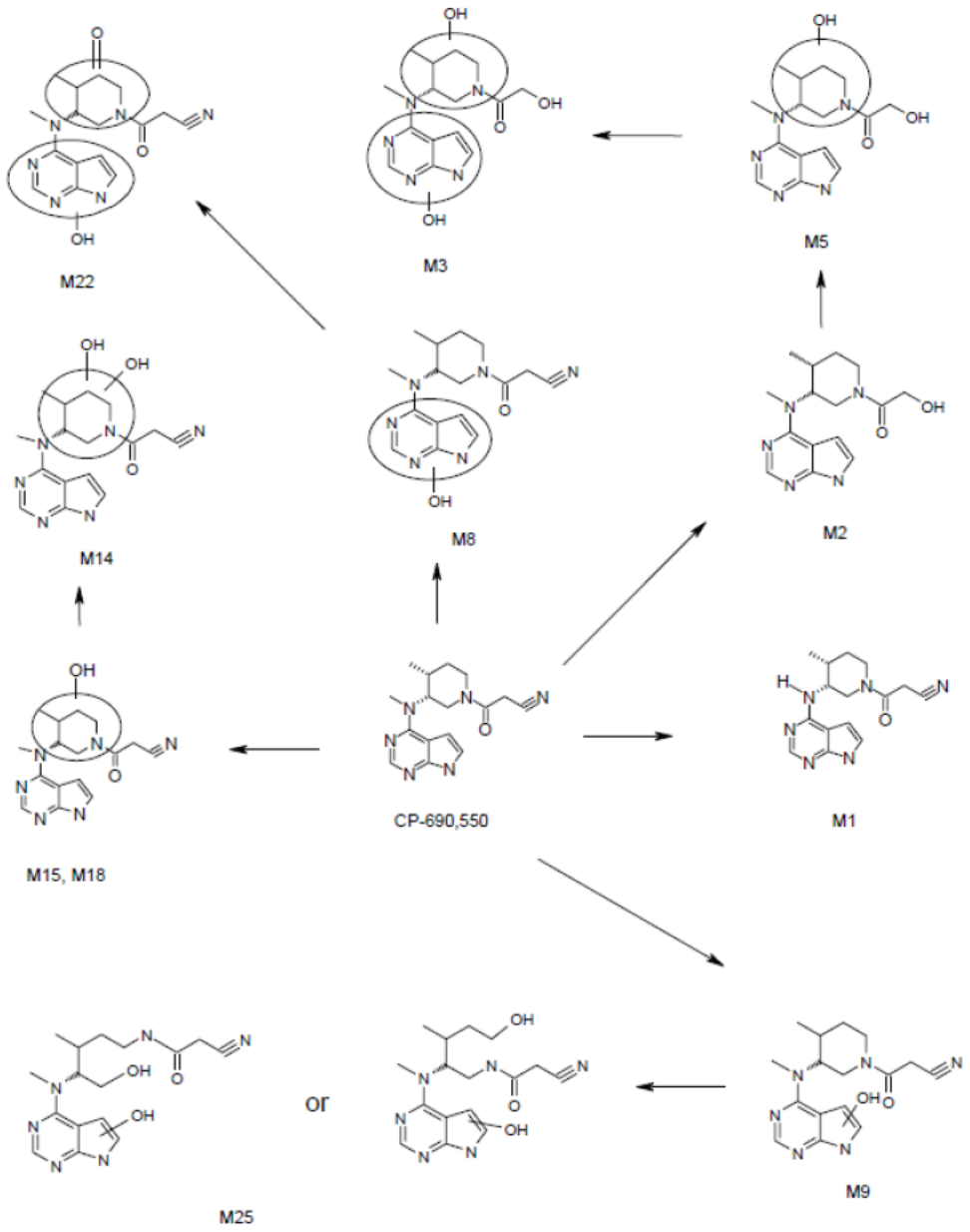

Figure 51: Proposed in vitro metabolic pathways of CP-690,550

Study # DM2007-690550-067

Title: Identification of Human Cytochrome P450 Isoforms Responsible for In Vitro Metabolism of CP-690,550

- **Objective:** To characterize the human CYP isoforms responsible for the *in vitro* metabolism of CP-690,550
- **Method:** [^{14}C] CP-690,550 was incubated with and without isoform-specific inhibitors to characterize the potential contribution of CYP450 isoforms to CP-690,550 metabolism. The inhibitors used and their concentrations were: furafylline

(10 μM for 1A2), sulfaphenazole (10 μM for 2C9), quinidine (1 μM for 2D6), (+)N-3-benzylnirvanol (10 μM for 2C19), and ketoconazole (1 μM for 3A)

- **Results and Conclusion:** The %inhibition of CP-690,550 metabolism in presence of different metabolites is shown in Figure 52. Formation of these metabolites was significantly reduced in the presence of ketoconazole (1 μM) indicating that CYP3A was primarily responsible for metabolism of CP-690,550.

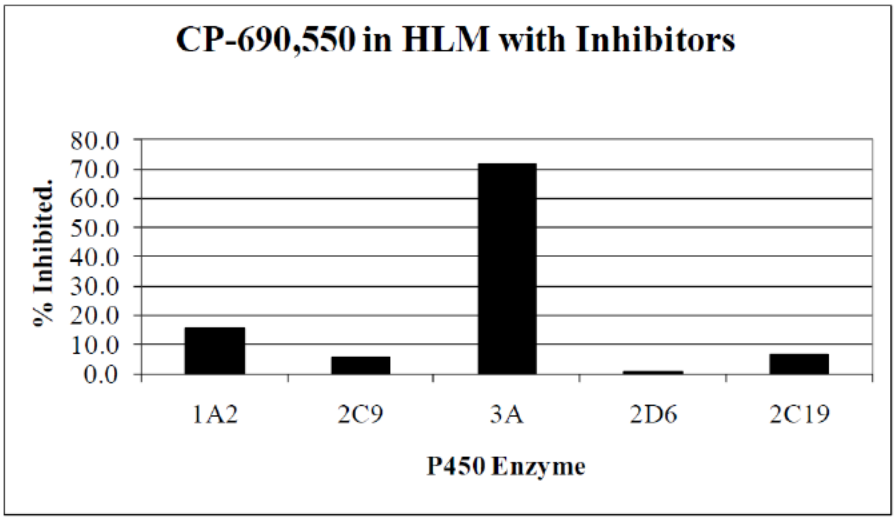

Figure 52: Percent inhibition of CP-690,550 (10 μM) human liver microsomal metabolism (30 minute incubation time and 1 mg/mL protein content) using various isoform selective chemical inhibitors

In vitro Enzyme Inhibition

Study # DM2001-690550-020

Title: Effect of CP-690,550 on Human Drug Metabolizing Enzymes *In Vitro*

- **Objective:** To determine the potential for CP-690,550 to inhibit human drug metabolizing enzymes *in vitro*
- **Method:** Standard marker activity substrates for different enzymes were incubated with pooled human liver microsomes (HL-MIX-13) in the presence of NADPH with CP-690,550 concentrations of 0 (control), 0.30, 3, and 30 μM.
- **Results and Conclusion:** Percent inhibition observed at 30 μM concentration of CP-690,550 is shown in Table 41. CP-690,550 demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A activities. IC_{50} values could not be calculated since CP-690,550 did not inhibit any activity more than 27%.

Table 41: Summary of IC50 Data for CP-690,550 in Human Liver Microsomes

Marker Substrate Activity	Enzyme	% of control at [I] = 30 μM	IC_{50} (μM) Mean ± SE
Phenacetin *O*-Deethylase	CYP1A2	100	>30
Bupropion Hydroxylase	CYP2B6	81	>30
Amodiaquine *N*-Deethylase	CYP2C8	95	>30
Diclofenac 4'-Hydroxylase	CYP2C9	81	>30
S-Mephenytoin 4'-Hydroxylase	CYP2C19	96	>30
Dextromethorphan *O*-Demethylase	CYP2D6	110	>30
Felodipine Oxidase	CYP3A	73	>30
Midazolam 1'-Hydroxylase	CYP3A	94	>30
Testosterone 6β-Hydroxylase	CYP3A	84	>30

In vitro Enzyme Induction

Study # DM2007-(b) (4)001

Title: An investigation of the potential for (b) (4) to induce CYP3A4 and CYP1A2 in human hepatocytes

- **Objective and Method:** To investigate the potential of (b) (4) to induce CYP3A4 and CYP1A2 *in vitro* using the immortalized human hepatocytes, the Fa2N-4 cell line, and cryopreserved human hepatocytes
- **Results and Conclusion:**

  CYP3A4

  Treatment of the Fa2N-4 cells with (b) (4) caused mild induction (1.2-2.5-fold) of CYP3A4 mRNA and testosterone 6β-hydroxylase activity at most concentrations tested between 0.78 and 100 μM compared to 3 to 10 fold induction with rifampin. The method with cryopreserved human hepatocytes showed dose dependent induction of CYP3A4 mRNA levels following treatment with (b) (4) (b) (4) in concentrations 6.25-100 μM compared to 7.7 fold induction following treatment with rifampin at 25 μM. However, clinically relevant concentrations (i.e., steady-state concentrations for 10 mg bid=0.31 μM) are much lower than 6.25 μM.

  CYP1A2

  Compared to omeprazole, an inducer of CYP1A2, no induction of ethoxyresorufin-O-deethylation (ethoxyresorufin is a specific substrate for CYP1A2 activity). In different assays, omeprazole caused 6.8-36 fold increase in CYP1A2 activity, while ratios of activity before and after treatment with (b) (4) remain close to 1.

PHARMACOKINETICS

1. Mass Balance Study

Study # A3921010

Title: Study to evaluate the metabolic profile and routes of excretion of [^{14}C] CP-690,550 in healthy male subjects

- **Objective:** The objective of this study was to evaluate the metabolic profile and the routes of excretion of [^{14}C]CP-690,550 in healthy male subjects
- **Study design:** non-randomized, open-label, single-dose study.
- **Test drug and sample size:** 50 mg oral dose of [^{14}C]CP-690,550 containing a radiolabel dose of approximately 163 µCi. N=6.
- **Samples:** CP-690,550 and its metabolites pharmacokinetics was evaluated from all/selected blood samples collected at 0 (just before dosing), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours postdose.
- **Results**

  The overall recovery of the administered dose was approximately 94%. Major portion of the radioactivity was recovered during the first 24 hours after dosing. Cumulative total, urine, and fecal recovery of CP-690,550 following oral administration is shown in Figure 53

Absorption:

Plasma concentrations for both CP-690,550 and total radioactivity peaked at 1 hr following oral administration. Mean Cmax value for parent drug was 397 ng/mL and for total radioactivity was 611 ng-eqiv/mL. $AUC_{0\text{-}inf}$ values for parent ranged from 977-2060 ng*h/mL and for total radioactivity it was 2430-4700 ng-eqiv*h/mL with a mean value of 3440 ng-eqiv*h/mL.

Metabolism:

- Percentage of total dose recovered as parent drug on metabolites in circulation, feces and urine are shown in Table 43,
-
- Table **44**, and Table 45, respectively.
- The major primary metabolic pathways of CP-690,550 included oxidation of the pyrrolopyrimidine ring (M8 and M9), oxidation of the piperidine ring (M18), piperidine ring side chain oxidation (M2 and M4) and glucuronidation (M20). A minor metabolic route was due to N-demethylation to form M1. The other metabolites were due to combination of these primary metabolic pathways.
- In addition to unchanged drug, a total of 7 metabolites were identified in feces by LC/MS/MS. The major fecal metabolites were two hydroxylated metabolites (M9, M18), 2-carboxy-ethanone (M4), 2-hydroxy-ethanone (M2) and two dihydroxylated metabolites (M11 and M14).
- A total of 10 metabolites were identified in urine by LC/MS/MS. The major urinary metabolites were hydroxylated metabolite (M9, 19.6%), 2-carboxy-ethanone (M4, 8.2%), 2-hydroxy-ethanone (M2, 3.6%) and its glucuronide (M29), two dihydroxylated metabolites (M11 and M14) and the CP-690,550 glucuronide (M20).

Elimination:

Major portion (approximately 80%) of the administered radioactivity was excreted in the urine, suggesting that urinary excretion was the primary route of elimination of CP-690,550 radioactivity in humans

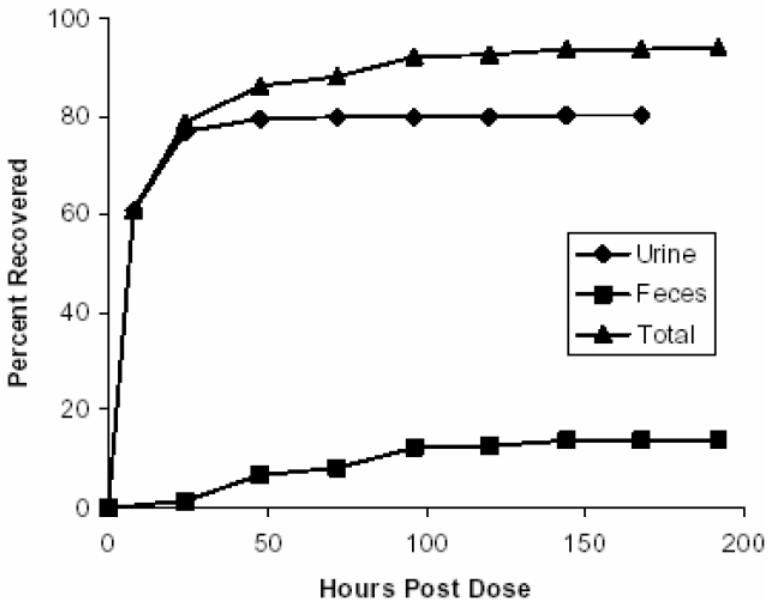

Figure 53: Cumulative Mean Recovery of Administered Radioactivity in Urine and Feces from Male Subjects over 192 Hours Following Oral Administration of a Single 50 mg Dose of [^{14}C]CP-690,550

Table 42: Percentage of Dose Excreted in Urine and Feces over 192 Hours by Male Subjects Following Oral Administration of a Single 50 mg Dose of [^{14}C]CP-690,550

Subject #	Subject ID	Urine	Feces	Total*
1	10011003	80.5	15.8	96.4
2	10011007	73.6	14.4	88.0
3	10011009	79.5	13.6	93.1
4	10011010	83.2	15.5	98.6
5	10011012	80.0	12.9	92.9
6	10011017	83.6	10.7	94.3
Mean		80.1	13.8	93.9
SD		3.6	1.9	3.6

Table 43: Percentage of Circulating Metabolites of CP-690,550 in Male Subjects Following Oral Administration of a Single 50 mg Dose of [^{14}C]CP-690,55

Metabolites	m/z	Ret. Time (min)	Percent of Dose							
			Subject #							
			1	2	3	4	5	6	Mean	SD
M14	345	8.3	3.2	0.7	1.1	4.5	3.3	6.2	3.2	2.1
M4	318	12.4	4.4	5.3	1.4	5.5	2.6	4.5	3.9	1.6
M20, M11, M29	489, 345, 480	15.1	4.8	8.0	4.7	7.5	5.8	6.6	6.2	1.4
M1, M2	299, 304	17.6	0.8	7.3	7.4	7.9	10.4	10.9	7.4	3.6
CP-690,550	313	20.8	77.5	69.5	77.1	57.4	73.8	61.1	69.4	8.5
M9	329	26.4	1.6	1.2	0.6	0.5	ND	ND	1.0	0.5

ND = Not detected

Table 44: Percentage of Fecal Metabolites of CP-690,550 in Male Subjects Following Oral Administration of a Single 50 mg Dose of [^{14}C]CP-690,550

Metabolites	m/z	Ret.Time (min)	Percent of Dose							
			Subject #							
			1	2	3	4	5	6	Mean	SD
M14	345	9.2	2.4	2.1	1.6	1.8	1.8	1.5	1.9	0.3
M18, M4	329, 318	12.6	3.8	2.9	2.1	4.3	4.5	3.0	3.4	0.9
M11	345	14.7	1.7	2.1	1.2	1.3	1.4	1.3	1.5	0.3
M2	304	17.1	0.7	0.4	0.7	0.5	0.5	0.4	0.5	0.1
CP-690,550	313	20.8	0.4	1.1	2.5	1.2	0.3	0.2	0.9	0.8
M9	329	27.0	1.9	1.6	2.0	1.8	1.1	1.0	1.6	0.4
M22	343	31.4	1.6	2.4	1.9	2.1	1.3	1.4	1.8	0.4
Unknown		34.0	3.2	1.8	1.7	2.4	2.0	1.9	2.2	0.6

Table 45: Percentage of Urinary Metabolites of CP-690,550 in Male Subjects Following Oral Administration of a Single 50 mg Dose of [^{14}C]CP-690,550

Metabolites	m/z	Ret.Time (min)	Percent of Dose							
			Subject #							
			1	2	3	4	5	6	Mean	SD
M14	345	11.2	3.1	4.4	2.3	3.7	3.2	4.7	3.5	0.9
M4	318	12.7	8.0	10.2	6.7	9.3	7.9	7.8	8.2	1.2
M20	489	14.9	2.3	3.2	1.7	2.2	1.2	2.6	2.2	0.7
M11, M29	345, 480	15.2	10.0	13.1	7.9	11.2	9.7	12.3	10.6	1.9
M1, M2	299, 304	18.1	3.6	3.1	3.4	3.8	3.8	3.9	3.6	0.3
CP-690,550	313	20.5	33.7	18.2	37.9	28.9	31.2	24.4	28.8	7.1
M31	320	23.3	1.2	1.3	0.8	1.3	1.4	2.4	1.4	0.5
M8	329	24.9	0.8	1.9	0.9	1.7	1.4	1.9	1.4	0.5
M9	329	27.3	17.8	18.3	18.0	21.2	20.2	23.6	19.6	2.2

2. Single Rising Dose (Oral)

Trial # A3921002

Title: Phase I, Double-Blind, Single Oral Dose, Placebo-Controlled, Cohort Dose Escalation Study to Evaluate the Safety, Toleration, Pharmacokinetics, and Pharmacodynamics of CP-690,550 in Healthy Volunteers

- **Objective:** This study had 3 objectives: (1) to characterize the safety and toleration of escalating single oral doses of CP-690,550 in healthy subjects, (2) to characterize the pharmacokinetics of escalating single oral doses of CP-690,550 in healthy subjects and (3) to characterize the pharmacodynamics of escalating single oral doses of CP-690,550 in healthy subjects
- **Study design:** randomized, double-blind (third party), parallel group, placebo-controlled, single-dose. At each dose level 8 subjects were randomized to CP-690,550 and 4 subjects were randomized to placebo. Blood and urine samples were collected up to 72 hours.

- **Test drug:** CP-690,550 in oral powder for constitution dosage form at doses 0.1, 0.3, 1, 3, 10, 30, 60, and 100 mg
- **Results:**
  - Mean serum CP-690,550 concentration vs. time profiles are shown in Figure 54. T_{max} was reached by 0.5 to 1 hour. CP-690,550 appears to follow mono-exponential disposition kinetics with parallel terminal phase for all tested dose levels. PK parameters for different dose levels are listed in Table 46. Terminal half-life of CP-690,550 was approximately 3 hours.
  - Systemic exposure of CP-690,550 increased with dose in a dose proportional manner resulting in approximately similar dose-normalized $AUC_{0\text{-inf}}$ values across tested dose levels (Figure 55), indicating linear pharmacokinetics.
  - Average renal clearance was about 136 mL/min and was slightly higher than the creatinine clearance, suggesting some active tubular secretion.

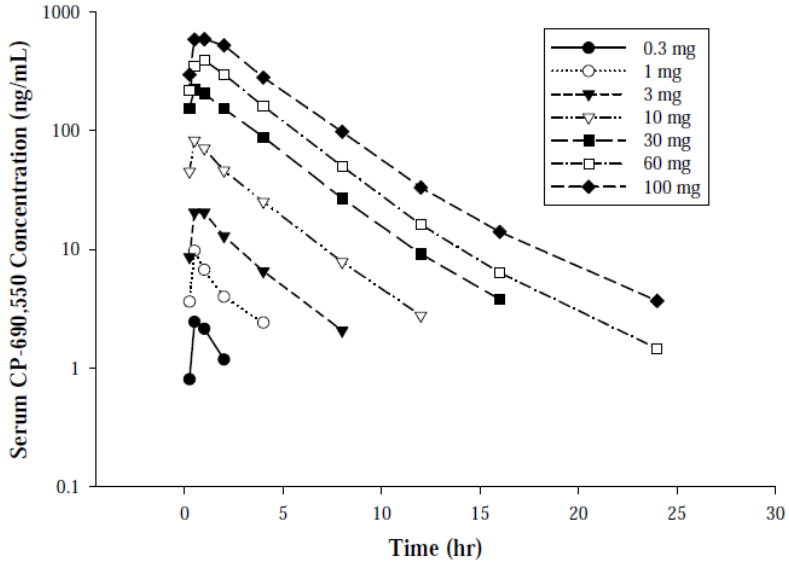

Figure 54: Mean Serum CP-690,550 Concentrations vs Times Following Administration of a Single Oral OPC Dose of CP-690,550 to Fasted Healthy Subjects

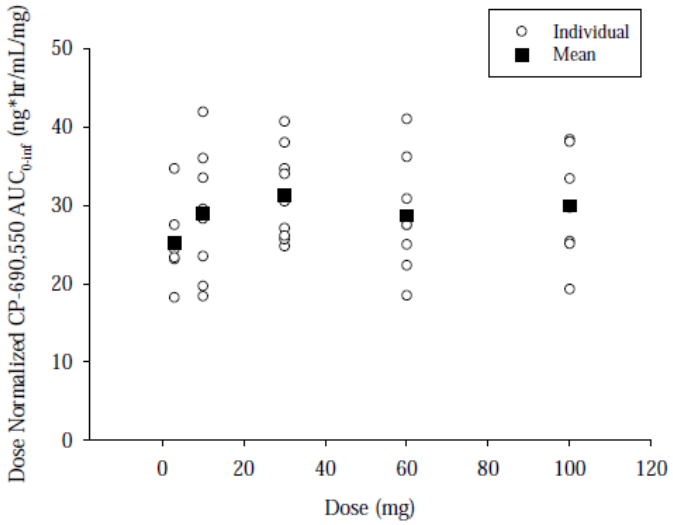

Figure 55: Dose Normalized CP-690,550 $AUC_{0\text{-}inf}$ Following Administration of a Single Oral OPC Dose (3 to 100 mg) of CP-690,550 to Fasted Healthy Subjects

Table 46: Mean (SD) Pharmacokinetic Parameters of CP-690,550 Following Administration of a Single Oral Dose of CP-690,550 OPC to Fasted Healthy Subjects

Dose group	$AUC_{0\text{-}Tlast}$ (ng*hr/mL)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	Cmax (ng/mL)	Tmax† (hr)	$T_{1/2}$ (hr)
0.1 mg N=8	0.158 (0.01)	NC	1.27 (0.082)	0.5 (0.5 – 0.5)	NC
0.3 mg N=8	3.91 (2.07)	NC	2.65 (0.619)	0.5 (0.5 – 1)	NC
1 mg N=8	19.2 (6.54)	NC	10.5 (2.28)	0.5 (0.5 – 1)	NC
3 mg N=8	69.5 (13.4)	75.5 (14)	21.8 (3.04)	0.5 (0.5 – 1)	2.31 (0.348)
10 mg N=8	283 (80.3)	289 (81.5)	88 (10.2)	0.5 (0.25 – 1)	2.61 (0.633)
30 mg N=9	933 (176)	938 (175)	240 (44.5)	0.5 (0.25 – 2)	2.72 (0.576)
60 mg N=8	1710 (435)	1720 (438)	408 (97.7)	1 (0.5 – 1)	2.68 (0.555)
100 mg N=7	2980 (709)	2990 (716)	638 (118)	0.5 (0.5 – 2)	3.07 (0.571)

†Median and Range are reported for Tmax

NC = Not Calculated, SD = Standard Deviation

3. Multiple Rising Dose (12 days)

Trial # A3921003

Title: Phase 1, Investigator-blind, Subject-blind, Sponsor-open, Placebo-controlled, Two-week, Multiple Dose Escalation Study in Medically Stable Subjects with Psoriasis to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of CP-690,550

- **Objective:** To evaluate the safety of CP-690,550 administered as multiple oral doses in subjects with Psoriasis. To evaluate the pharmacokinetics of CP-690,550 administered as multiple oral doses to subjects with psoriasis. To assess changes in biochemical and cell markers and cytokine expressions.
- **Study design:** Randomized, double-blind within dose group, placebo controlled
- **Test drug and sample size:** 5, 10, 20 and 30 mg oral powder in capsule (OPC), and 50 and 60 mg tablet (N=4 to 9)
- **Results:** Tofacitinib PK characteristics after multiple dose administration were consistent with that observed after single dose. T_{max} was reached within 0.5-1 hr, mean apparent terminal $t_{1/2}$ ranged from 2.3 – 4.3 hrs. Accumulation after multiple dose was

minimal as expected based on short half-life and BID dosing regimen. Mean plasma PK profiles are shown in Figure 56 and summary PK parameters are listed in Table 47.

The urine PK parameters are listed in Table 48. The mean unbound renal clearances were slightly higher than the glomerular filtration rates for all cohorts. The mean percent of administered dose excreted unchanged in urine ranged from 18.3%-27.2%.

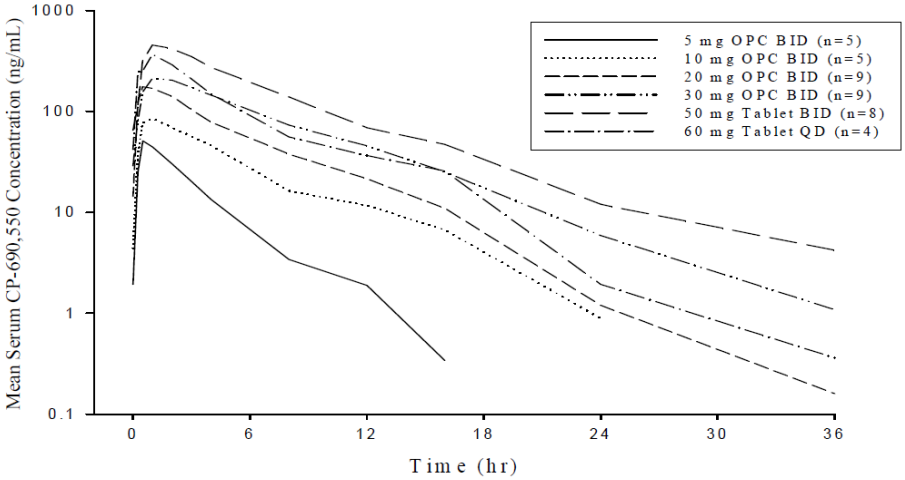

Figure 56: Mean Serum CP-690,550 Concentrations Versus Time on Day 14 Following Multiple Oral Dosing with CP-690,550 in Medically Stable Subjects with Psoriasis

Table 47: Arithmetic Mean (SD) CP-690,550 Serum Pharmacokinetic Parameters on Days 1 and 14 Following Multiple Oral Dosing with CP-690,550 in Medically Stable Subjects with Psoriasis

Cohort	C_{max} ng/mL		$AUC_{0\text{-}tau}$ ng·h/mL		R_{ac}	T_{max} h[a]		t1/2 hr
	Day 1	Day 14	Day 1	Day 14	Day 14/Day 1	Day 1	Day 14	Day 14
5 mg OPC BID (n=5)	48.3 (24.5)	50.9 (21.2)	161 (86.1)	154 (80.3)	0.974 (0.181)	0.50 (0.25-1.00)	0.50 (0.50-0.50)	2.26 (0.518)
10 mg OPC BID (n=5)	90.5 (20.4)	87.7 (13.2)	349 (34.7)	422 (49.5)	1.22 (0.203)	0.50 (0.50-1.00)	1.00 (0.50-1.00)	3.93 (0.456)
20 mg OPC BID (n=9)	212 (62.3)	194 (53.9)	732 (232)	850 (216)	1.22 (0.389)	0.50 (0.25-2.00)	0.50 (0.25-2.00)	3.61 (0.548)
30 mg OPC BID (n=9)	180 (53.1)	225 (43.9)	860 (235)	1350 (308)	1.62 (0.343)	0.50 (0.50-3.00)	1.00 (0.50-4.00)	4.30 (0.884)
60 mg Tablet QD (n=9[b])	429 (99.1)	403[b] (133)	1720 (453)	1780[b] (501)	1.14[b] (0.176)	1.00 (0.50-2.00)	1.00[b] (0.50-2.00)	NR[b]
50 mg Tablet BID (n=8)	457 (88.2)	568 (205)	2120 (837)	2600 (1580)	1.16 (0.270)	1.00 (0.50-3.00)	1.00 (0.50-2.00)	3.92 (1.36)

[a] Median (Range) reported for tmax
[b] Only 4 subjects had calculable data on Day 14 in the 60 mg Tablet QD cohort
NR: Not reported due to insufficient data
Source: Tables 5.2.1, 5.2.4 – 5.2.6

Table 48: Mean (SD) CP-690,550 Urine Pharmacokinetic Parameters Following 14 Days of Multiple Oral Dosing with CP-690,550 in Medically Stable Subjects with Psoriasis

Cohort	A_E (mg)	A_E / Dose (%)	CL_R (mL/min)	CL_R / Fu (mL/min)
5 mg OPC BID (n=4[a])	1.22 (0.471)	24.3 (9.41)	130 (55.9)	224 (96.4)
10 mg OPC BID (n=5)	2.63 (0.739)	26.4 (7.40)	103 (20.2)	178 (34.8)
20 mg OPC BID (n=9)	4.82 (4.41)	24.1 (22.1)	88.5 (60.7)	153 (105)
30 mg OPC BID (n=9)	7.05 (3.38)	23.5 (11.3)	88.0 (45.0)	152 (77.5)
60 mg Tablet QD (n=4[b])	11.0 (3.63)	18.3 (6.04)	109 (45.2)	188 (77.9)
50mg Tablet BID (n=8)	13.6 (6.46)	27.2 (12.9)	99.5 (43.1)	172 (74.2)

[a] 1 subject was excluded in the 5 mg OPC BID cohort due to insufficient data
[b] 5 subjects were excluded in the 60 mg Tablet QD cohort due to insufficient data
A_E = total amount of parent drug excreted in 12 of 24 hours ; A_E / Dose = A_E / $AUC_{0\text{-}tau}$; CL_R = renal clearance; CL_R / Fu = renal clearance of unbound drug, where Fu was determined from in vitro human protein binding data[3].
Source: Table 5.2.8

SPECIFIC POPULATION

4. Renal impairment (PK study)

Trial # A3921006

Title: Phase 1, Open-Label Study to Evaluate Single Dose Pharmacokinetics, Safety, and Tolerability of CP-690,550 in Patients with Impaired Renal Function

- **Objective:**
  - To evaluate the pharmacokinetics of CP-690,550 administered orally as a single dose in subjects with impaired renal function, compared to healthy subjects.
  - To evaluate the safety and tolerability of CP-690,550 administered orally as a single dose in subjects with impaired renal function
- **Study design:** Open-label, parallel-group phase I trial
- **Treatment groups and sample size:**
  Patients were allocated to renal function groups by rate of creatinine clearance (CLcr) calculated using Cockcroft-Gault method, as follows:

Table 49: Classification of renal function as reported by sponsor

Group	Description	Estimated Creatinine Clearance (mL/min)	Number of Subjects
1	Normal renal function	>80 mL/min	6
2	Mild renal impairment	>50 and ≤80 mL/min	6
3	Moderate renal impairment	≥30 and ≤50 mL/min	6
4	Severe renal impairment	<30 mL/min	6

Reviewer's comments:

- Sponsor's classification of renal function (as shown in Table 49) was differed from than the classification suggested in FDA's renal guidance[4] in terms of CLcr

[4] Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010).

cut-offs. FDA's guidance indicate CLcr ≥ 90 mL/min as normal renal function, between 60-89 as mild renal impairment, between 30-59 as moderate renal impairment, between 15-29 as severe renal impairment and <15 not requiring dialysis or requiring dialysis as end stage renal disease (ESRD). For the results discussed below, patients were re-grouped based on FDA guidance.

- In calculation of CLcr using Cockcroft-Gault method sponsor used ideal body weight instead of actual body weight. It is acceptable given that there were some obese study subjects (mean BMI across groups ranged from 24.2 – 41.1 kg/m^2). However, there is no consensus on whether ideal body weight is the right parameter to replace actual body weight in this situation.

- **Duration of Treatment:** Single Dose
- **PK Sampling Schedule**
  - **Blood –** Day 1 at 0 (just prior to dosing), 0.5, 1, 1.5, 2, 4, 8, 10, 12, 16, 24 and 48 hours after dosing
  - **Urine –** for 24 hours starting on Day 1 at the time of dosing and ending on Day 2, 24 hours after Day 1 dosing
- **Results:**
  - Following re-grouping of patients based on FDA's classification of renal function, there were 3 subjects in normal function, 8 subjects in mild, 7 subjects in moderate, and 6 subjects in severe renal impairment group.
  - The geometric mean ratio and 95% CI for comparison of PK parameters for renally impaired subjects vs. normal renal function are shown in Table 50.
  - Mean percentage change in AUC (90%CI), for subjects with mild, moderate, and severe renal impairment compared to normal renal function were respectively: 41% (-5%, 109%), 71% (14%, 157%), and 156% (69%, 287%). Mean percentage changes in Cmax (90% CI) for these cases were respectively: 1% (-31%, 49%), 2% (-31%, 52%), and 21% (-19%, 81%).
  - On continuous scale of CLcr, there was an increase in AUCinf with decline in renal function (Figure 57)
  - Measured unbound renal clearance for almost all subjects was greater than the individual estimated CLcr (Figure 58), suggesting that active tubular secretion may be playing some role in renal excretion of CP-690,550.

Reviewer's comments

- Mean plasma concentration data for different renal function groups were modeled using WinNonlin and simulations were performed to identify the optimum dosing based on exposure matching for each renal function group. For details on the dosing recommendations please check the Clinical Pharmacology review.

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http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf

Table 50: Geometric mean ratio and 90% CI for comparison of PK parameters between renally impaired subjects vs. normal renal function

	Test	Reference	GM Ratio [%Ref]	CI_90_lower	CI_90_Upper
AUC	Mild	Normal	140.92	94.81	209.48
	Moderate	Normal	171.43	114.45	256.78
	Severe	Normal	255.73	169.04	386.89
C_{max}	Mild	Normal	101.29	68.87	148.98
	Moderate	Normal	102.46	69.15	151.83
	Severe	Normal	120.65	80.64	180.53

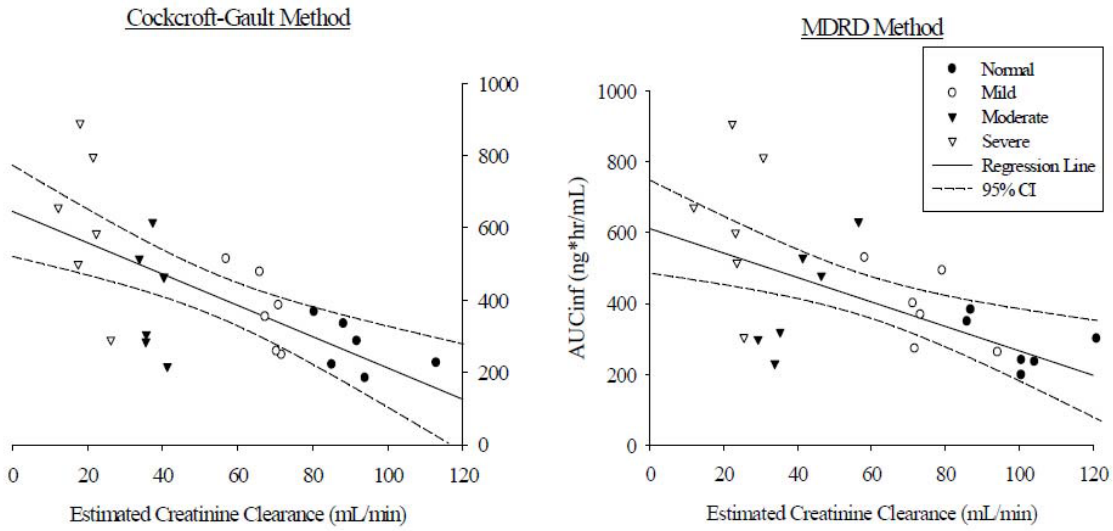


Figure 57: Individual AUC0-inf vs. estimated creatinine clearances following a single 10 mg dose of CP-690,550 in subjects with normal renal function, and in subjects with mild, moderate, and severe renal impairment (Sponsor reported).

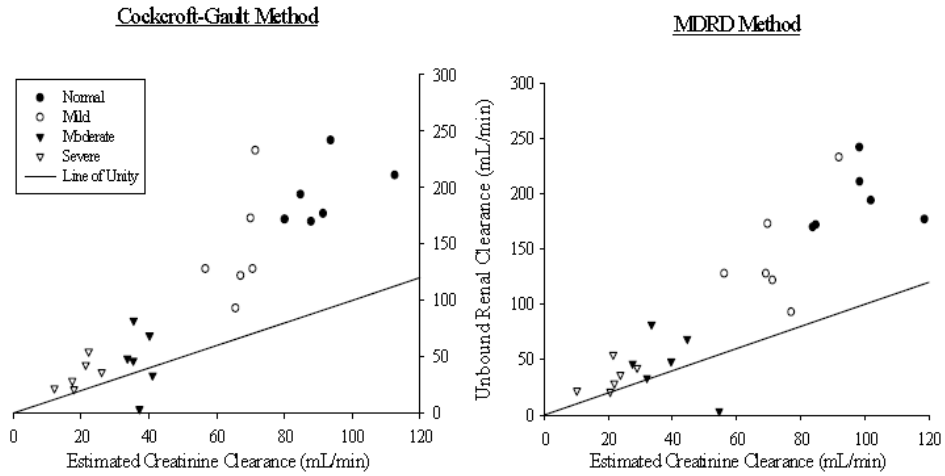


Figure 58: Individual CP-690,550 Unbound Renal Clearance (CLR/Fu) Levels Versus Estimated Creatinine Clearances Following A Single 10 mg Oral Dose of CP 690,550 in

subjects with normal renal function, and in subjects with mild, moderate, and severe renal impairment

- **Conclusions:**

No dose adjustment recommended for subjects with mild renal impairment. Check clinical pharmacology review for dosing recommendations in subjects with moderate and severe renal impairment.

5. PK in ESRD

Trial # A3921004

Title: Phase 1, Open-Label Study of the Pharmacokinetics, Non-Renal Clearance and Dialyzability of CP-690,550 in Subjects with End-Stage Renal Disease Undergoing Hemodialysis

- **Objective:**
  - To evaluate the pharmacokinetics and non-renal clearance of CP-690,550 administered as a single oral dose in subjects with end stage renal disease (ESRD) undergoing hemodialysis
  - To assess the degree to which CP-690,550 is dialyzable
  - To evaluate the safety of CP-690,550 administered as a single oral dose in subjects with ESRD undergoing hemodialysis
- **Study design:** Open-label, 2-period phase I study
- **Treatment groups:**
  - Period 1 (N=12): 10 mg of CP-690,550 oral powder for constitution (OPC) administered as a single oral dose 1 to 2 hours after completion of hemodialysis;
  - Period 2 (N=11): 10 mg of CP-690,550 OPC administered as a single oral dose approximately 4 hours prior to hemodialysis.
- **Duration of Treatment:** Single Dose
- **PK Sampling Schedule**
  - **Blood –**
  - Period 1 - Days 1-2: 0 (just prior to dosing), 0.25, 0.5, 1, 2, 3, 4, 8, 12, 16, and 24 hours after dosing; Day 3: 48 hours after dosing (before hemodialysis), and then paired arteriovenous samples at the mid-point of each 1-hour dialysate sampling period (during hemodialysis), at the end of hemodialysis, and at 2 and 4 hours after the end of hemodialysis
  - Period 2 – Day 1: Before dosing, before hemodialysis, and then paired arteriovenous samples at the mid-point of each 1-hour dialysate sampling period (during hemodialysis), at the end of hemodialysis, and at 2 and 4 hours after the end of hemodialysis; Day 2: 24 hours after dosing; Day 3: 48 hours after dosing
- **Results:**

The plasma concentration time profile of CP-690,550 from first stage in ESRD subjects is shown in Figure 59. Rapid absorption and elimination of CP-690,550 were observed in ESRD subjects, suggesting extensive non-renal clearance. The terminal half-life was approximately 3.5 hours. The AUC and C_{max} in ESRD subjects were 37% and 20% higher than that observed for the same OPC formulation in study A3921002 (Table 46).

Data from second period, in which CP-690,550 was administered 4 hours prior to dialysis, were used to measure the dialyzability of CP-690,550. CP-690,550 was highly dialyzable during hemodialysis based on observed dialyzer clearance and efficiency in ESRD subjects. A substantial amount of CP-690,550, i.e., about 73% of the amount that was excreted through renal pathway, was extracted into the dialysate (Table 52). The dialyzer clearance of CP-690,550 remained consistent within each subject over the duration of the hemodialysis session (Figure 60). However, there was considerable inter-subject variability in dialyzer clearance, ranging from 174 to 527 mL/min (Figure 60).

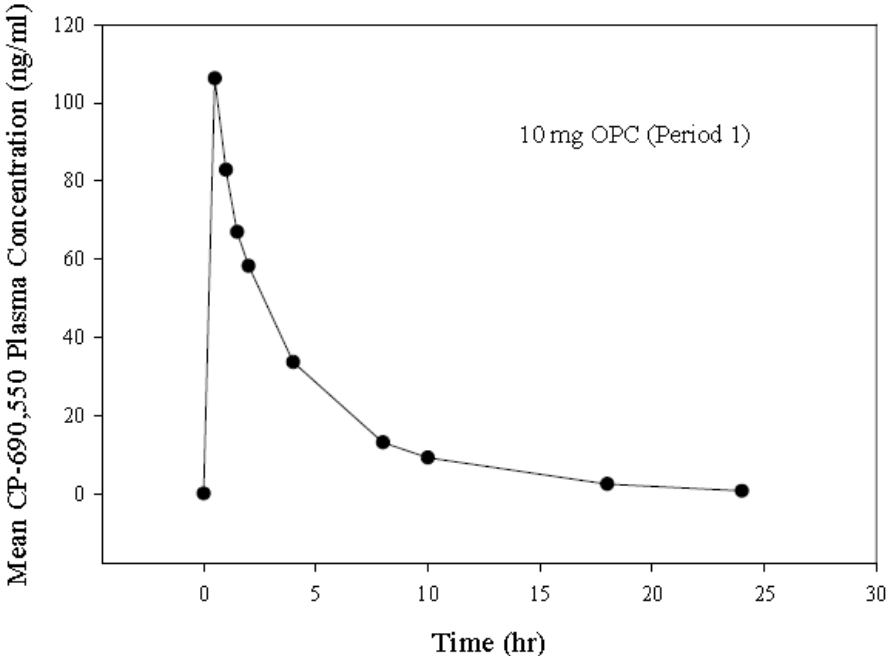


Figure 59: Mean Plasma CP-690,550 Concentrations Over Time Following administration of single dose of 10 mg CP-690,550 in end stage renal disease patients (period 1)

Table 51: Arithmetic Mean (SD) of Plasma CP-690,550 Pharmacokinetic Parameters in subjects with ESRD (period 1)

	AUC_{0-inf} (ng·h/mL)	C_{max} (ng/mL)	T_{max}[a] (h)	$t_{1/2}$ (h)	CL_{po} (mL/min)
N	12	12	12	12	12
Mean (SD)	396 (158)	106 (23.9)	0.5 (0.5 – 0.5)	3.46 (1.18)	501 (243)

[a] Median (range) reported for T_{max}.

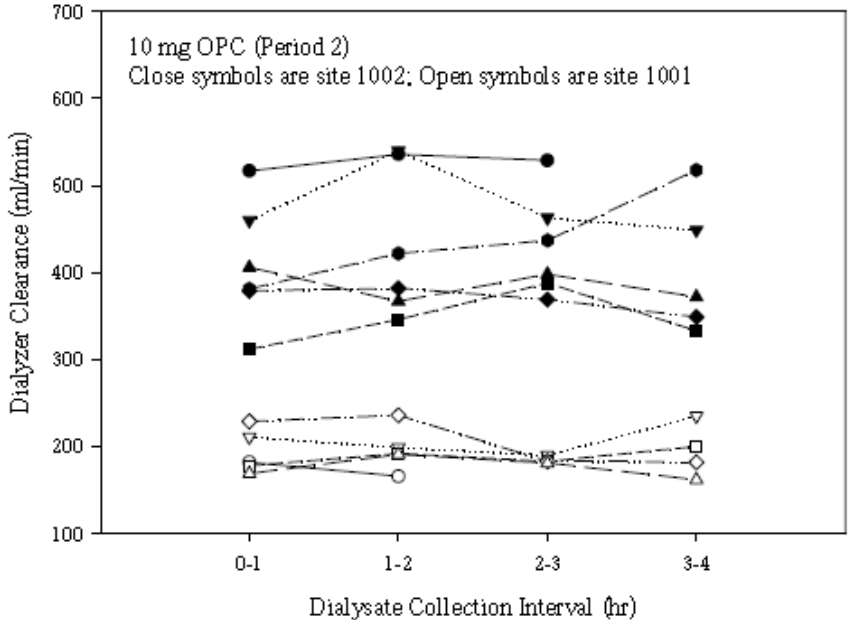


Figure 60: Individual Dialyzer Clearance of CP-690,550 over Dialysate Collection Intervals Following Administration of a Single Dose of 10 mg CP-690,550 OPC 4 Hours Prior to hemodialysis in subjects with ESRD (Period 2)

Table 52: Arithmetic Mean (SD) of CP-690,550 Pharmacokinetic parameters in subjects with ESRD (period 2)

	CL_{HD} (mL/min)	Qb (mL/min)	E
N	11	11	11
Mean (SD)	318 (132)	423 (113)	0.73 (0.15)
% CV	41.5	26.6	20.5

CL_{HD} – dialyzer clearance in each dialysate collection period
Q_b – blood flow entering dialyzer
E – dialyzer efficiency (CL_{HD}/Q_b)

- **Conclusions:**

Substantial proportion of CP-690,550 is cleared through non-renal pathway.
Of the amount that is cleared through renal pathway, about 73% is extracted during dialysis.

6. Measured GFR

Trial # A3921033

Title: A Phase 1, Randomized, Sponsor-Open, Placebo-Controlled, Trial to Evaluate the Effect of Multiple-Dose Treatment with CP-690,550 on Glomerular Filtration Rate as Measured by Iohexol Serum Clearance in Healthy Volunteers

- **Objective:**

To evaluate the effect of CP-690,550 on glomerular filtration rate (GFR), measured by iohexol serum clearance (CL), when administered to healthy volunteers for 14 days.
The secondary objectives were to evaluate the effect of CP-690,550 on serum creatinine (sCr), creatinine clearance (CrCL) as measured by 24-hour urine collections, estimated glomerular filtration rate (eGFR) as calculated by the Cockcroft-Gault equation, 24-hour urinary protein excretion, effective renal plasma flow as measured by para-aminohippuric acid (PAH) serum CL; on total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, lipoprotein(a), apoprotein A-I, apoprotein B, ratio of HDL/LDL, and ratio of apoprotein B/apoprotein A-I; and on blood pressure; and to characterize the steady-state pharmacokinetics of CP-690,550.

- **Study design:** Open-label, placebo-controlled study in healthy subjects
- **Treatment groups:**
  - Period 1 (N=12): 10 mg of CP-690,550 oral powder for constitution (OPC) administered as a single oral dose 1 to 2 hours after completion of hemodialysis;
  - Period 2 (N=11): 10 mg of CP-690,550 OPC administered as a single oral dose approximately 4 hours prior to hemodialysis.
- **Duration of Treatment:** 14 days with either CP-690,550 3 x 5 mg tablets twice daily (BID) or matching placebo 3 tablets BID followed by approximately 29 days in follow-up
- **PK Sampling Schedule**
  - **Blood –** Day 14: prior to dosing, 0.5, 1, 2, 4, 8, 12 hrs
- **PD Sampling Schedule**
  - **Iohexol serum clearance –** day 1, day 8, day 15
  - **PAH renal clearance –** day 1, day 8
  - **CrCL –** 24 hr urine collections at day 0 to day 1, day 7 to day 8, day 14 to day 15
- **PD Parameters Calculation**
  - Iohexol serum clearance values were calculated for each subject by noncompartmental analysis of concentration-time data.
  - Renal clearance (CLr) of PAH was calculated as:

    $$= UPAH \cdot V / PPAH$$

    (where UPAH = urine concentration of PAH, V = urine excretion rate, and PPAH = serum concentration of PAH).
  - Serum creatinine (SCr) was determined at the end of the 24-hour urine collection interval, and used for calculating the CrCL using Cockcroft-Gault equation.
- **Results:**

The adjusted geometric mean ratios for various endpoints and comparisons were within 0.9 to 1.1 with reasonably narrow CIs (Table 53). These results demonstrate that 14-day treatment with CP-690,550 has no effect on GFR, renal secretion of creatinine or ERPF in healthy volunteers.

- **Conclusions:**

Results suggest that kidney function is preserved at least following 14 days of treatment with tofacitinib.

Table 53: Summary of results for Iohexol Serum Clearance, CrCL and PAH renal clearance

	Ratios of Adjusted Geometric Means (90% CI)		
	Day15 / Day1 ratio for CP-690,550	Day15 / Day1 ratio for placebo	Ratio of Day15 / Day1 ratio for CP-690,550 to Day15 / Day1 ratio for placebo
Iohexol Serum Clearance	0.995 (0.942, 1.05)	0.911 (0.846, 0.982)	1.09 (0.997, 1.20)
CrCL	0.948 (0.893, 1.01)	0.905 (0.856, 0.956)	1.05 (0.967, 1.14)
PAH Renal Clearance	0.925 (0.819, 1.04)	0.946 (0.779, 1.15)	0.978 (0.783, 1.22)

CI = confidence interval, CrCL = creatinine clearance, PAH = para-aminohippuric acid

7. Hepatic Impairment

Trial # A3921015

Title: A Phase 1, Non-Randomized, Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of CP-690,550 in Subjects with Hepatic Impairment and Normal Hepatic Function

- **Objective:**

To compare the pharmacokinetics (PK) of CP-690,550 in subjects with mild and moderate hepatic impairment to subjects with normal hepatic function

Note –

A significant portion of tofacitinib is cleared through hepatic metabolism; therefore, tofacitinib was not evaluated in patients with severe hepatic impairment because potential for high systemic exposures may pose the risk of immuno-suppression in patients who are already at risk of infection from their hepatic disease.

- **Study design:** Open-label, nonrandomized, single-treatment, single-dose
- **Treatment groups:**
  - healthy normal liver function (N=6)
  - mild hepatic impairment (N=6)
  - moderate hepatic impairment (N=6)
- **PK Sampling Schedule**
  - **Blood –**0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 hrs
- **Pharmacogenomic evaluation**
  - Blood sample was collected on day 0 for genotyping
- **Results:**

The geometric mean PK parameter values following administration of 10 mg dose in subjects with hepatic impairment and normal hepatic function are summarized in Table 54. Subjects with mild hepatic impairment had no significant change in AUC and C_{max}

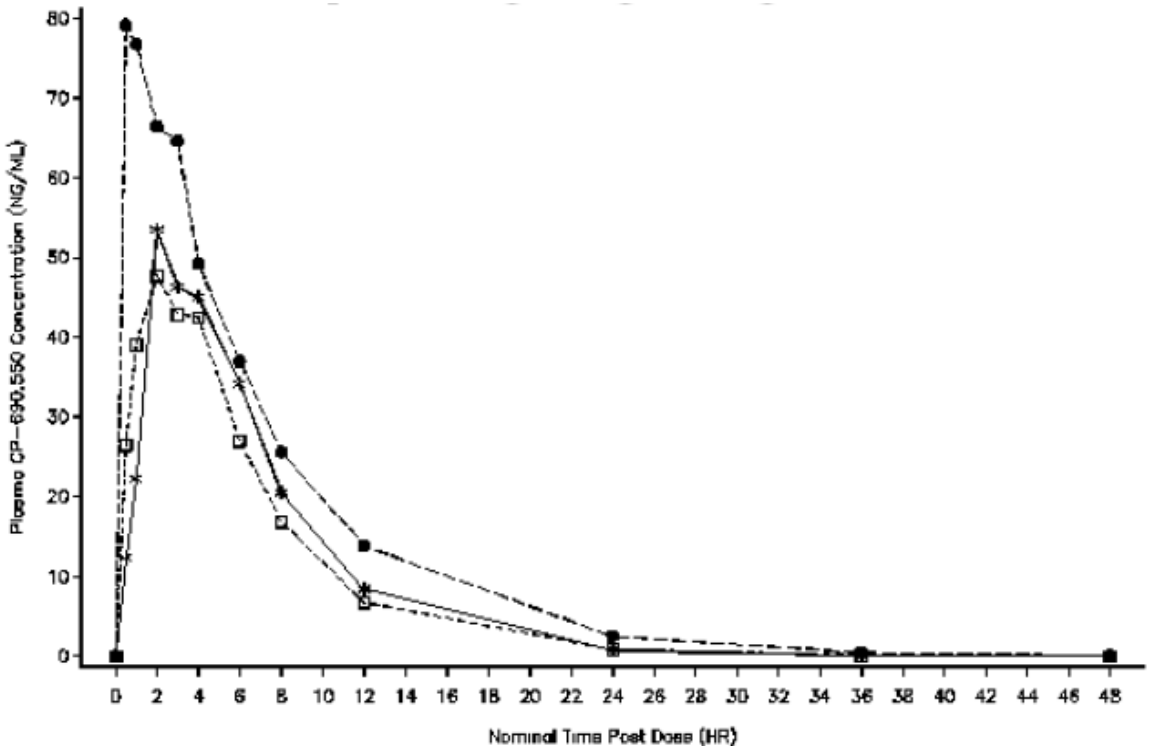
Table 55). Subjects with moderate hepatic impairment had 65% increase in AUC and 49% increase in C_{max} (Table 55).

- **Conclusions:**

No dose adjustment recommended for subjects with mild hepatic impairment.

Reviewer's comments

- Mean plasma concentration data for different hepatic function groups were modeled using WinNonlin and simulations were performed to identify the optimum dosing based on exposure matching for moderate hepatic impairment group. For details on the dosing recommendations please check the Clinical Pharmacology review.



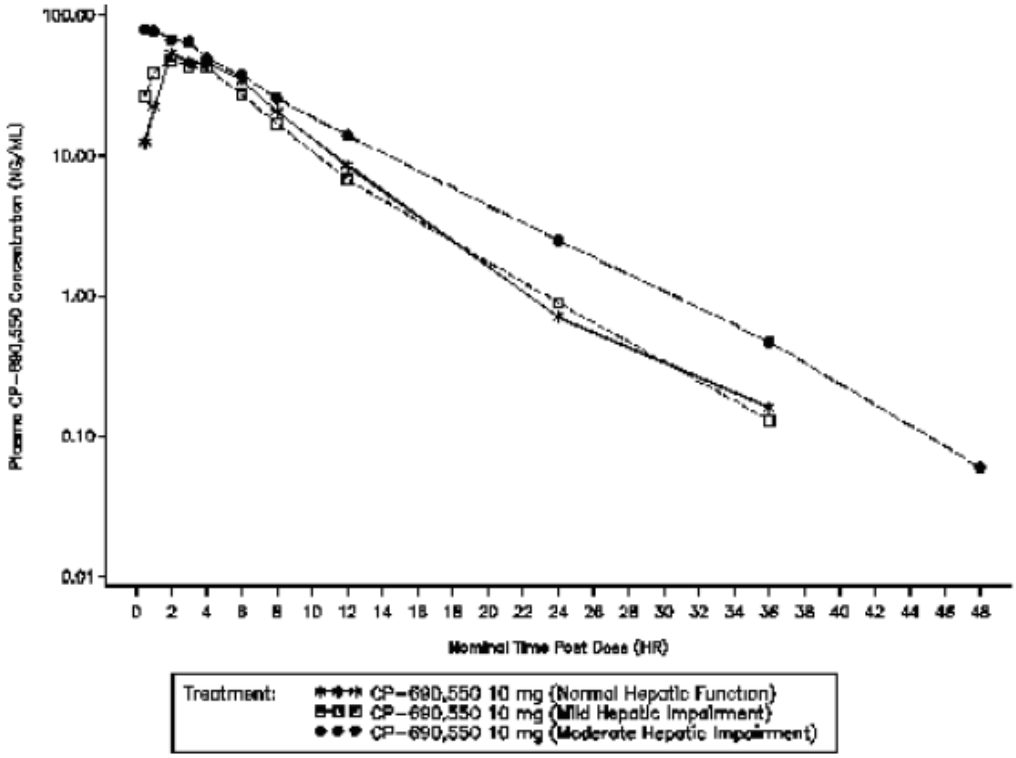


Figure 61: Median Plasma CP-690,550 Concentration-Time Profiles by Hepatic function group following a single 10 mg oral dose

Table 54: Descriptive Summary of Plasma CP-690,550 Pharmacokinetic Parameter values following a single 10 mg oral dose

Parameter (units)	Parameter Summary Statistics[a] by Hepatic Impairment Group		
	Normal Hepatic Function	Mild Impairment	Moderate Impairment
N	6	6	6
AUC_{inf} (ng.hr/mL)	354.8 (23)	366.0 (15)	583.9 (45)
AUC_{last} (ng.hr/mL)	353.5 (23)	364.3 (15)	581.1 (45)
C_{max} (ng/mL)	60.45 (23)	60.08 (27)	89.92 (33)
T_{max} (hr)	3.00 (1.00-6.03)	2.50 (0.500-4.00)	0.750 (0.500-2.00)
t½ (hr)	4.092 (23)	4.365 (9)	5.413 (20)

Source: Table 13.5.2

Abbreviations: AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), C_{max} = maximum observed concentration, CV = coefficient of variation, N = number of subjects, t½ = terminal half-life, T_{max} = time for C_{max}

[a] Geometric mean (%CV) for all except: median (range) for T_{max}; arithmetic mean (%CV) for t½.

Table 55: Summary of Statistical Comparisons: Mild and Moderate Hepatic impairment groups vs. normal hepatic function group

Parameter, units	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Test	Reference		
Mild hepatic impairment (test) vs normal hepatic function (reference)				
AUC_{inf}, ng.hr/mL	366.0	354.8	103.15	78.31, 135.85
AUC_{last}, ng/mL	364.3	353.5	103.06	78.21, 135.81
C_{max}, ng/mL	60.08	60.45	99.39	75.01, 131.70
Moderate hepatic impairment (test) vs normal hepatic function (reference)				
AUC_{inf}, ng.hr/mL	583.9	354.8	164.57	124.95, 216.75
AUC_{last}, ng/mL	581.1	353.5	164.38	124.74, 216.62
C_{max}, ng/mL	89.92	60.45	148.75	112.26, 197.11

Source: Table 13.5.3.1
Abbreviations: AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}), CI = confidence interval, C_{max} = maximum observed concentration
[a] The ratios (and 90% CIs) are expressed as percentages.

DRUG-DRUG INTERACTIONS

8. DDI with Ketoconazole

Trial # A3921054

Title: A Phase 1, Open Label, Fixed-Sequence Study to Estimate the Effect of Ketoconazole on the Pharmacokinetics of Tasocitinib (CP-690,550) in Healthy Volunteers

- **Objective:**

To estimate the effect of ketoconazole oral administration on the PK of a single 10 mg oral dose of CP-690,550

- **Study design and treatment schedule:** Open-label, single fixed sequence, 2-period design (N=12) (see Table 56)

Table 56: Study design for A3921054

Period	Day *	Treatment
1	Day 1	CP-690,550 10 mg (2 x 5 mg tablets, single dose)
2	Day 1	ketoconazole 400 mg (2 x 200 mg tablets) q24h
	Day 2	ketoconazole 400 mg (2 x 200 mg tablets) q24h
	Day 3	ketoconazole 400 mg (2 x 200 mg tablets) q24h PLUS CP-690,550 10 mg (2 x 5 mg tablets, single dose)
	Day 4	No treatment given (Discharge)

Source: Section 16.1.1
* Note: Day is relative to the first day of dosing for each period. Day 1 of Period 2 will start immediately after the 24 hours postdose sample in Period 1 is collected.
q24h = every 24 hours.

Reviewer's comment:

Tofacitinib's half-life is ~3 hrs, which is comparable or shorter than the half-life of ketoconazole, i.e., ~3-5 hrs; therefore, the given schedule of ketoconazole 400 mg QD is sufficient (and perhaps better than 200 mg BID) in achieving the inhibition of CYP3A4

enzymes in liver and intestine[5]. Moreover, since single-dose of ketoconazole is likely to maintain more than 50% inhibition of intrinsic clearance of both organs for up to 10 hours[2], it would cover the majority of the elimination phase of tofacitinib.

- **PK Sampling Schedule**

Blood –0, 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 hrs in Periods 1 (Days 1) and 2 (Days 3 and 4)

- **Results:**

Coadministration with ketoconazole increased C_{max} and slowed down the clearance (increased terminal half-life) of CP-690,550 (Figure 62). CP-690,550 AUC increased by ~103% and C_{max} increased by ~16% following coadministration with ketoconazole (Table 57).

Conclusions:

When coadministered with ketoconazole, tofacitinib exposure increased by ~103%.

Reviewer's Comments:

- Mean plasma concentration data for tofacitinib with and without ketoconazole were modeled using WinNonlin and simulations were performed to identify the optimum dosing based on exposure matching for tofacitinib coadministration with ketoconazole. For details on the dosing recommendations please check the Clinical Pharmacology review.

[5] Ping Zhao et al. Quantitative Evaluation of Pharmacokinetic Inhibition of CYP3A Substrates by Ketoconazole: A Simulation Study. Journal of Clinical Pharmacology. ***2009;49:351-359***

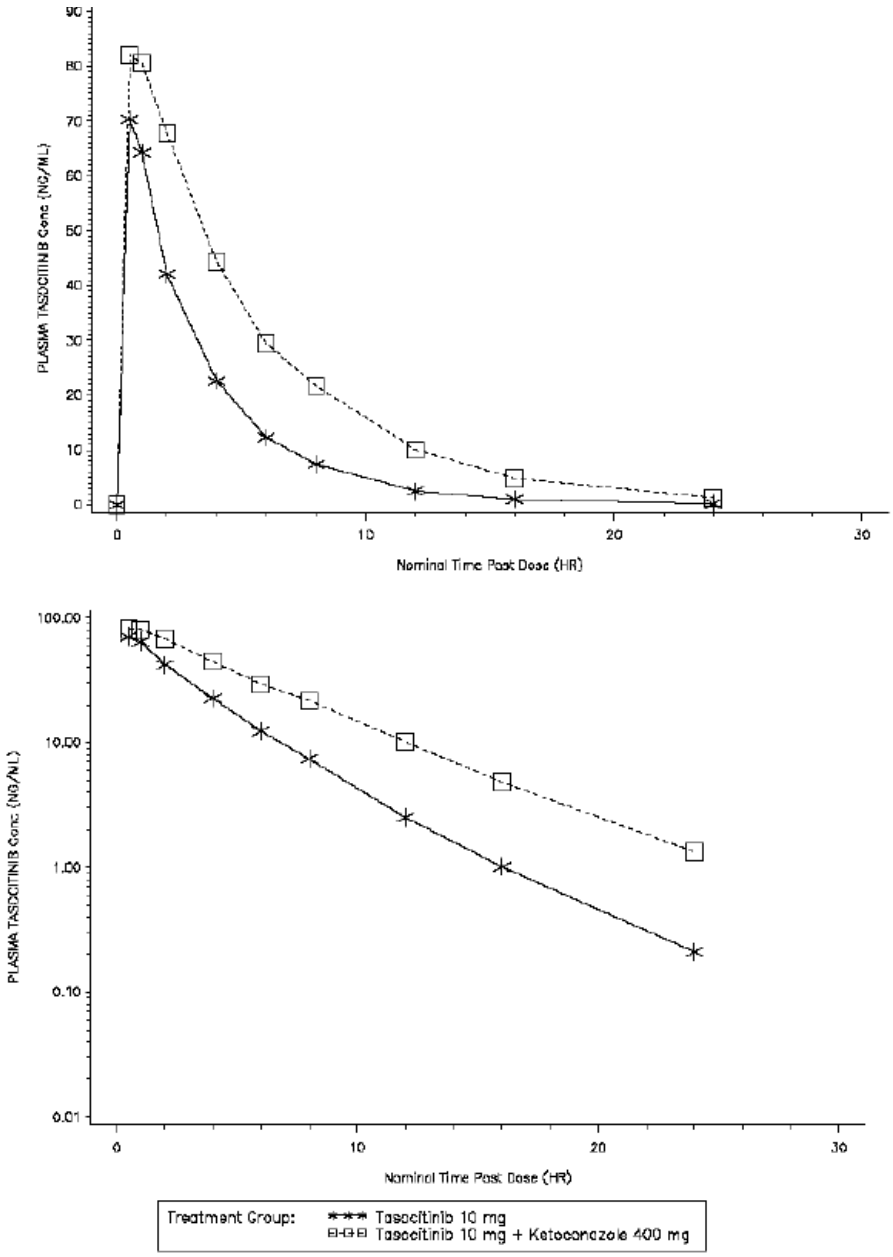


Figure 62: Median plasma CP-690,550 concentration-time profiles following single oral 10 mg dose alone and with multiple-dose ketoconazole

Table 57: PK parameters and statistical summary for comparison of plasma CP-690,550 with and without ketoconazole

Parameter (units)	Adjusted Geometric Means: Test (CP-690,550 10 mg + Ketoconazole 400 mg)	Adjusted Geometric Means: Reference (CP-690,550 10 mg)	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
AUC_{inf} (ng.hr/mL)	488.4	240.3	203.23	190.96, 216.30
AUC_{last} (ng.hr/mL)	481.0	239.2	201.08	189.28, 213.61
C_{max} (ng/mL)	91.61	78.81	116.24	104.59, 129.18

AUC_{inf} = area under the plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed concentration.
[a] The ratios (and 90% CIs) are expressed as percentages.

9. DDI with Fluconazole

Trial # A3921014

Title: A Phase 1, Open Label, Single Fixed-Sequence, Crossover Study to Estimate the Effect of Fluconazole on the Pharmacokinetics, Safety and Tolerability of CP-690,550 in Healthy Adult Subjects

- **Objective:**

To estimate the effect of multiple dose fluconazole on the pharmacokinetics of a single oral dose of CP-690,550 in healthy subjects

- **Study design and treatment schedule:** open-label, single fixed-sequence, crossover, single-dose CP-690,550, multiple-dose fluconazole design (see Table 58)

Table 58: Study design for A3921014

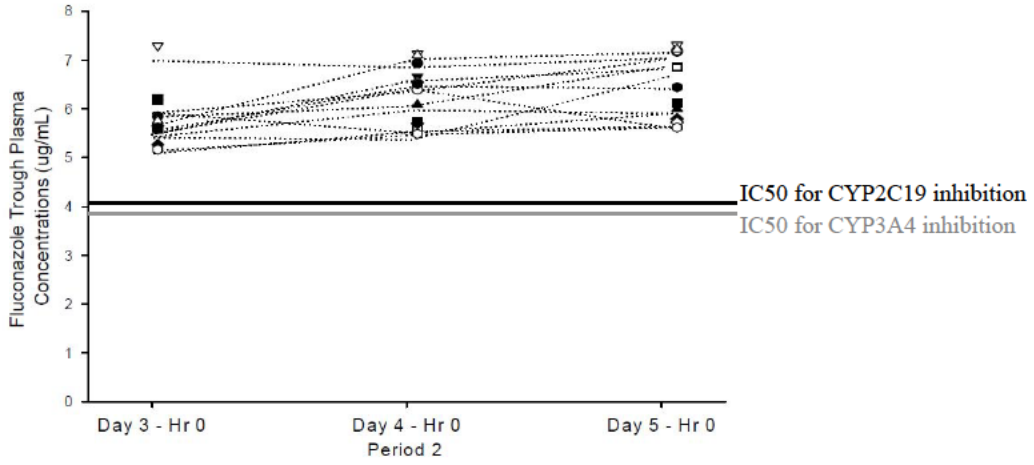
Period	Day*	Treatment
1	Day 1	CP-690,550 30 mg (single dose)
	Day 2	Washout (No treatment given)
	Day 3	Washout (No treatment given)
2	Day 1	Fluconazole 400 mg QD
	Day 2	Fluconazole 200 mg QD
	Day 3	Fluconazole 200 mg QD
	Day 4	Fluconazole 200 mg QD
	Day 5	Fluconazole 200 mg QD PLUS CP-690,550 30 mg (single dose)
	Day 6	Fluconazole 200 mg QD
	Day 7	Fluconazole 200 mg QD
	Day 8	No treatment given (discharge)
Follow-up	Follow-up visit was 7-30 days after the last dose of CP-690,550	

*Note: Day is relative to the first day of dosing for each period.
QC = once daily

Reviewer's comment:

Fluconazole is a moderately potent inhibitor of CYP3A4 and a strong inhibitor of CYP2C19[6] and is a commonly used medication for the treatment of fungal infections in transplant recipients. Since CP-690,550 is metabolized via hepatic clearance by means of both CYP3A and CYP2C19, this study provides important information about use of tofacitinib.

Typical clinical dose of fluconazole is 200 mg/day or less, which is also the maintenance dose used in this study. A loading dose of 400 mg/day was given on day 1, which is recommended in fluconazole prescribing information to achieve plasma concentrations close to steady-state by the second day of therapy[7]. As shown in Figure 63, with the dosing regimen used in this study, fluconazole concentrations were at steady-state by day 4. The fluconazole concentrations reached in this study (>5 μg/mL, see Figure 63) were higher than the IC_{50} values for CYP3A4 (i.e., 12.3 μM or 3.84 μg/mL) and CYP2C19 (i.e., 13.1 μM or 4.1 μg/mL) inhibition[8], indicating that fluconazole doses were sufficient to evaluate the effect of CYP3A4 and CYP2C19 inhibition.



Hr 0 = Just prior to the fluconazole dose on that particular day
Source: Table B5.2.1.2

Figure 63: Individual trough plasma concentrations of fluconazole on days 3-5 following a loading dose of fluconazole (400 mg) on day 1 and maintenance doses (200 mg QD) on days 2-7

- **PK Sampling Schedule**

PK analysis of CP-690,500

[6] Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. (February 2012 FDA draft guidance) http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf
[7] DIFLUCAN prescribing information. Accessed May 23, 2012. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/019949s055,019950s059,020090s038lbl.pdf
[8] Toshiro Niwa et al. Effect of Antifungal Drugs on Cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4 Activities in Human Liver Microsomes. Biol. Pharm. Bull. 28(9) 1805-1808 (2005).

Plasma- 0, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, 48 and 72 hours after dosing in Period 1 (Days 1) and Period 2 (Day5)

- **Results:**

Coadministration with fluconazole increased C_{max} and AUC and slowed down the clearance (increased terminal half-life) of CP-690,550 (Figure 64). CP-690,550 AUC increased by ~79% and C_{max} increased by ~27% following coadministration with fluconazole (Table 59).

- **Conclusions:**

When coadministered with fluconazole, tofacitinib exposure increased by ~79%.

Reviewer's Comments:

- Mean plasma concentration data for tofacitinib with and without fluconazole were modeled using WinNonlin and simulations were performed to identify the optimum dosing based on exposure matching for tofacitinib coadministration with fluconazole. For details on the dosing recommendations please check the Clinical Pharmacology review.

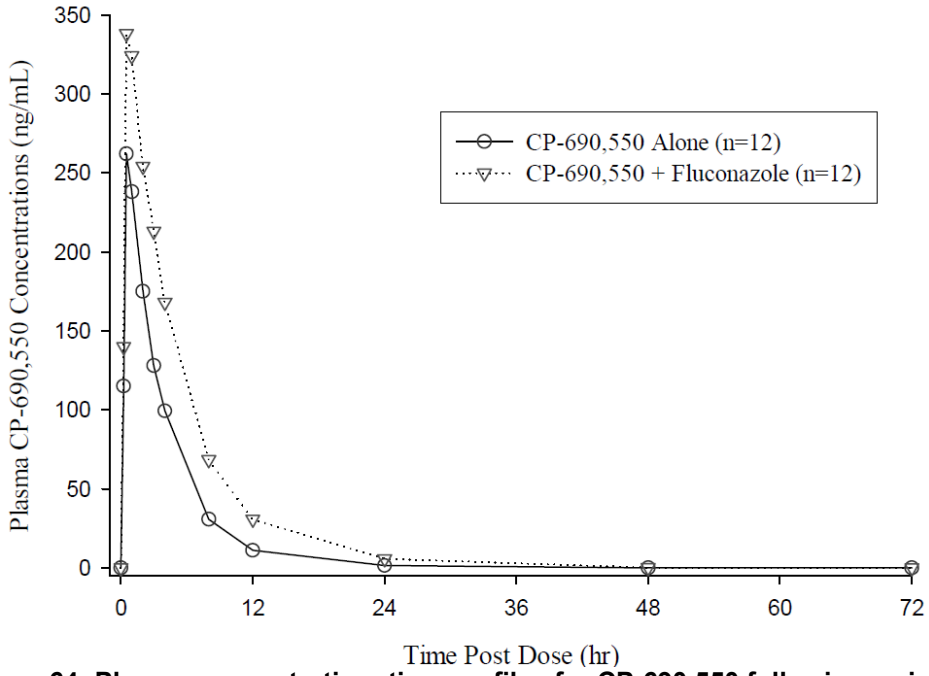


Figure 64: Plasma concentration -time profiles for CP-690,550 following a single 30 mg dose of CP-690,550 alone or in combination with fluconazole (fluconazole at steady-state)

Table 59: PK parameters for CP- 690,550 when given alone or in combination with fluconazole (fluconazole at steady-state) as a single 30 mg oral dose and statistical summary for comparison

Parameter (Units)	Adjusted Geometric Means		Ratio (%) T/R*	90% Confidence Intervals
	CP-690,550 + Fluconazole	CP-690,550 Alone		
AUC_{last} (ng·hr/mL)	1743.87	981.06	177.75%	162.43%, 194.53%
AUC_{inf} (ng·hr/mL)	1768.73	986.71	179.26%	163.81%, 196.16%
C_{max} (ng/mL)	350.85	276.82	126.74%	111.82%, 143.66%

* Ratio of adjusted geometric means between Test (T) (CP-690,550 + fluconazole) and Reference (R) (CP-690,550)
Source data: Table 13.5.3

10. DDI with Rifampin

Trial # A3921056

Title: A Phase 1, Open Label, Fixed-Sequence Study to Estimate the Effect of Repeat-Dose Rifampin on the Pharmacokinetics of CP-690,550 in Healthy Volunteers

- **Objective:**

To evaluate the effect of rifampin oral administration on the PK of a single 30 mg oral dose of CP-690,550

- **Study design and treatment schedule:** Open-label, single fixed sequence, 2-period design with repeat-dose of rifampin and single-dose of CP-690,550 (see Table 60)

Table 60: Study design for A3921056

Period	Day *	Treatment
1.	Day 1	CP-690,550 30 mg (single dose) as 6x5 mg tablets
2.	Day 1	Rifampin 600 mg q24h
	Day 2	Rifampin 600 mg q24h
	Day 3	Rifampin 600 mg q24h
	Day 4	Rifampin 600 mg q24h
	Day 5	Rifampin 600 mg q24h
	Day 6	Rifampin 600 mg q24h
	Day 7	Rifampin 600 mg q24h
	Day 8	CP-690,550 30 mg (single dose) as 6x5 mg tablets
	Day 9	No treatment given (Discharge)

Source: Section 16.1.1
*Note: Day is relative to the first day of dosing for each period. Day 1 of Period 2 was the same day as Day 2 of Period 1.
q24h = every 24 hours.

Reviewer's comment:
Rifampin dosing at 600 mg QD for multiple days is considered adequate for CYP3A4 induction and is preferred over use of lower doses. Inducers may take several days to exert their effects on enzyme activity and dosing for several days ascertains that enzyme induction is achieved before evaluating its effect on PK of CP-690,550.

- **PK Sampling Schedule**

Plasma – 0, 0.5, 1, 2, 4, 6, 8, 12, 16 and 24 hours in Period 1 (Day 1) and Period 2 (Day 8)

- **Results and Conclusions:**

Coadministration with rifampin significantly decreased AUC by 84% and C_{max} by 74%. (Figure 65 and

Table **61**). These low exposures may not be efficacious therefore coadministration of CP-690,550 with rifampin is not recommended.

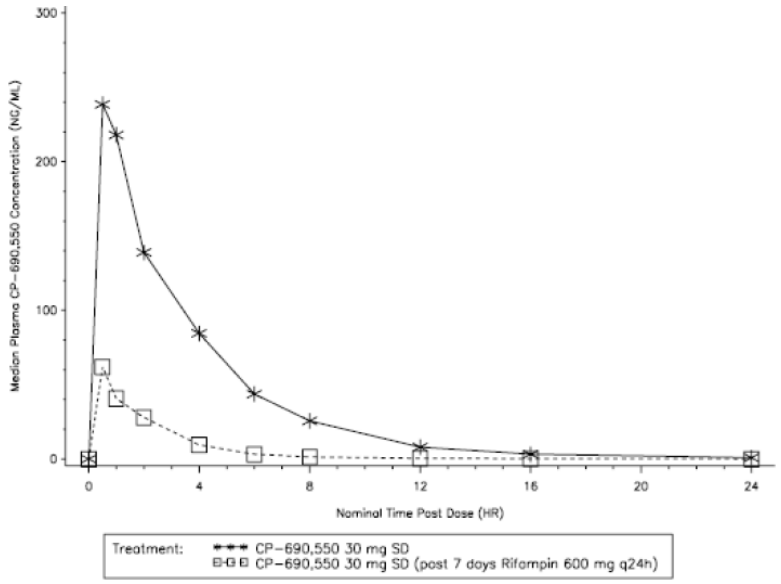


Figure 65: Median CP-690,550 Plasma Concentration-Time Profiles Following administration of CP-690,550 alone or post 7 days of rifampin 600 mg QD

Table 61: PK parameters for CP-690,550 following coadministration with and without rifampin and statistical summary for treatment comparisons

Pharmacokinetic Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratios	
	Test*	Reference*		Lower	Upper
AUC_{inf} (ng·hr/mL)	136.6	848.1	16.10	14.24	18.20
AUC_{last} (ng·hr/mL	135.2	841.7	16.07	14.36	17.98
C_{max} (ng/mL)	65.67	249.5	26.32	22.63	30.61

Source: Table 14.4.3.3

*Test = CP-690,550 30 mg SD after 7 days of rifampin 600 mg q24h; Reference = CP-690,550 30 mg SD alone

Pharmacokinetic parameters are defined in Table 4.

CI = confidence interval; q24h = every 24 hours.

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

11. DDI with Methotrexate

Trial # A3921013

Title: A Phase 1, Open Label Study of the Pharmacokinetics of Multiple Doses of Oral CP-690,550 and Single Doses of Oral Methotrexate in Rheumatoid Arthritis Subjects

- **Objective:**
  - To estimate the effects of methotrexate (MTX) on the pharmacokinetics (PK) of CP-690,550 when administered to subjects with rheumatoid arthritis (RA)
  - To estimate the effects of multiple doses of CP-690,550 (30 mg every 12 hours [q12h]) on the PK of MTX

- **Study design –** Open-label, non-randomized, fixed-sequence in subjects who had a diagnosis of RA for at least 6 months and were receiving a stable weekly oral MTX dose (15-25 mg/week) for a minimum of 28 days (see Table 62)

Table 62: Study design for A3921013

Day 1	Day 2	Days 3-6	Day 7	Days 8 & 9
MTX individualized SD	No treatment	CP-690,550 30 mg q12h	CP-690,550 30 mg (morning dose only) AND **MTX** individualized SD (5 minutes after CP-690,550)	No treatment

MTX = methotrexate; mg = milligrams; q12h = every 12 hours; SD = single dose.

- **PK Sampling Schedule**

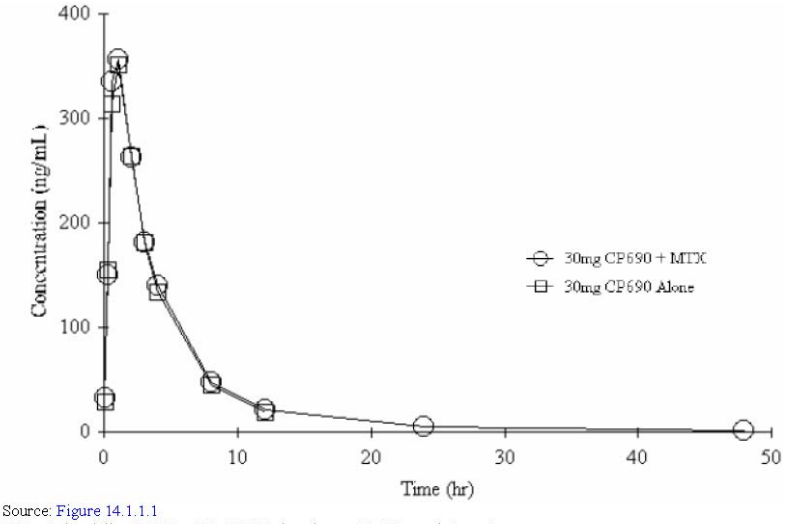
For Methotrexate - Plasma – day 1 to 3 – up to 48 hrs and day 7 – up to 48 hrs
For CP-690,550 - Plasma – day 6 – up to 12 hrs and day 7 – up to 48 hrs

- **Results**

Coadministration with methotrexate had no significant effect on plasma concentration – time profile of CP-690,550 (Figure 66). Vice-versa, coadministration with CP-690,550 also did not have any impact on plasma concentration – time profile of methotrexate (Figure 67). Geometric mean ratios and 90% CI for plasma PK parameters (AUC, Cmax) as well as amount of unchanged drug excreted in urine (Ae_{12}) and renal clearance (CL_R) were all within 0.8 to 1.25 for comparison of CP-690,550 given with methotrexate vs. CP-690,550 given alone (Table 63). For a similar comparison of methotrexate, geometric mean ratio was within 0.8-1.25 for comparison of PK parameters; however, lower bound of 90% CI was slightly lower than 0.8. There was relatively higher variability in urine PK parameters (Ae_{24} and CL_R) with 23% lower Ae_{24} and 14% lower CL_R following coadministration with CP-690,550 than given alone. These slight decreases in AUC and C_{max} were statistically significant; however, the extent of changes is not considered clinically significant.

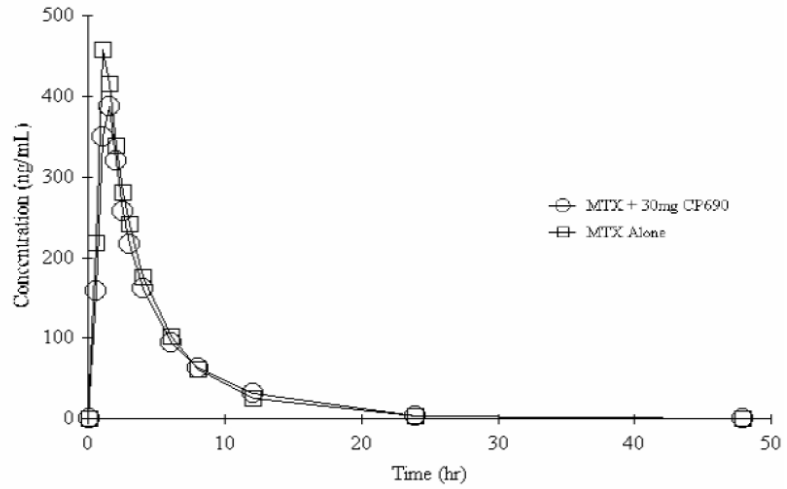
- **Conclusions:**

No dose adjustment recommended when CP-690,550 is coadministered with methotrexate and vice-versa no changes in methotrexate dosing are recommended following coadministration with CP-690,550.



Source: Figure 14.1.1.1
BID = twice daily; CP690 = CP-690,550; hr = hours; MTX = methotrexate.

Figure 66: Mean CP-690,550 plasma concentration vs. time profile following multiple dosing with CP-690,550 alone and in combination with methotrexate



Source: Figure 14.1.1.2
BID = twice daily; CP690 = CP-690,550; hr = hours; MTX = methotrexate

Figure 67: Mean methotrexate plasma concentration vs. time profile following a single oral dose of methotrexate alone and in combination with CP-690,550

Table 63: Statistical Analyses of Pharmacokinetic Parameters of CP-690,550

Parameters	Test (T)	Reference (R)	Adjusted Geometric Means		Ratio (%) T/R	90% Confidence Interval (%)	
			Test	Reference		Lower	Upper
AUC_{12} (ng·h/mL)	C	B	1344.12	1304.20	103.06	99.00	107.29
C_{max} (ng/mL)	C	B	374.26	364.39	102.71	93.79	112.47
CL/F (mL/hr)	C	B	21301.1	21931.4	97.13	92.60	101.87
Ae_{12} (mg)	C	B	6.25	6.32	98.91	87.92	111.26
CL_R (mL/hr)	C	B	4.65	4.85	95.88	86.01	106.88
			Adjusted Means		Difference T-R		
$t_{1/2}$ (hr)	C	B	3.18	2.64	0.54	0.21	0.87
			Medians				
T_{max} (hr)	C	B	1.00	1.00	0.00	-0.25	0.25

Source: Tables 13.5.3.1.1, 13.5.3.1.2, 13.5.3.1.3 and Appendices A10.2.1-A10.2.7
T = test; R = reference; AUC_{0-12} = area under the concentration time curve from 0 to 12 hours postdose; C_{max} = maximum serum concentration; CL/F = oral clearance; Ae_{12} = amount of unchanged drug excreted into urine from 0 to 12 hours postdose; CL_R = renal clearance of drug; T_{max} = time to C_{max}; $t_{1/2}$ = terminal phase half-life; MTX = methotrexate.
Test and Reference labels: B = CP-690,550 30 mg; C = CP-690,550 30 mg + MTX individualized dosing (15-25 mg).

Table 64: Statistical Analyses of Pharmacokinetic Parameters of methotrexate

Parameters	Test (T)	Reference (R)	Adjusted Geometric Means		Ratio (%) T/R	90% Confidence Interval (%)	
			Test	Reference		Lower	Upper
AUC_{24} (ng·h/mL)	C	A	1570.19	1753.89	89.53	77.38	103.57
C_{max} (ng/mL)	C	A	408.36	468.06	87.25	76.03	100.12
CL/F (mL/hr)	C	A	10329.5	9329.73	110.72	95.20	128.75
Ae_{24} (mg)	C	A	12.39	16.08	77.04	54.17	109.58
CL_R(L/hr)	C	A	7.88	9.16	86.06	59.06	125.42
			Adjusted Means		Difference T-R		
$t_{1/2}$ (hr)	C	A	3.36	2.87	0.50	0.23	0.76
			Medians				
T_{max} (hr)	C	A	1.25	1.00	0.25	0.00	0.25

Source data: Tables 13.5.3.2.1, 13.5.3.2.2, 13.5.3.2.3 and Appendices A10.3.1-A10.3.7
T = test; R = reference; MTX = methotrexate; AUC_{24} = area under the concentration time curve from 0 to 24 hours postdose; C_{max} = maximum serum concentration; CL/F = oral clearance; Ae_{24} = amount of unchanged drug excreted into urine from 0 to 24 hours postdose; CL_R = renal clearance of drug; T_{max} = time to C_{max}; $t_{1/2}$ = terminal phase half-life.
Test and Reference labels: A = MTX individualized dosing; C = CP-690,550 30 mg + MTX individualized dosing.

15. DDI with Tacrolimus and Cyclosporine

Trial # A3921020

Title: A Phase 1, Open Label, Fixed-Sequence Study to Estimate the Effect of Tacrolimus and Cyclosporine on the Pharmacokinetics of CP-690,550 in Healthy Volunteers

- **Objective:**
  - To estimate the effect of multiple dose tacrolimus (Tac) and cyclosporine (CsA) on the pharmacokinetics (PK) of a single oral (PO) dose of CP-690,550 in healthy volunteers

- **Study design and treatment schedule:**
  - Open-label, single, fixed sequence, 2-period, 2-cohort study (Cohort A – Tac; Cohort B – CsA) (see Table 65).
  - In period 2, subjects started with Tac 5 mg or CsA 200 mg dose. On day 3 of period 2, pre-dose Tac and CsA levels were measured using a rapid turn around

assay. If the day 3 pre-dose levels were supratherapeutic, doses were reduced based on pre-set criteria. And if the levels were subtherapeutic, doses were increased based on pre-set criteria.

- **PK Sampling Schedule**
  - In both Cohorts A and B, PK samples for analysis of CP-690,550 were drawn on day 1.
  - In presence of interacting drug, PK samples for CP-690,550 were drawn on day 8 in Cohort A and on day 6 in Cohort B.

- **Results**

Changes in plasma concentration – time profiles of CP-690,550 following coadministration with Tac and CsA are shown in Figure 68 and Figure 69, respectively. With Tac there was a slight slowing down of clearance of CP-690,550, which resulted in approximately 20% increase in AUC with no significant change in C_{max}.

With CsA there was relatively larger decrease in clearance of CP-690,550, which resulted in approximately 73% increase in AUC along with 17% decrease in C_{max}.

- **Conclusions**

Although PK interaction is assessed in this DDI study, there is also potential of pharmacodynamic drug-drug interaction between toacitinib and Tac and tofacitinib and CsA, because all of these drugs are immunosuppresants. The potential for these PD interactions has not been evaluated in clinical studies. For details on the dosing recommendations please check the Clinical Pharmacology review.

Table 65: Study design for A3921020

Period	Day[a]	Treatment: Cohort A	Treatment: Cohort B
1	Day 1	CP-690,550 10 mg (single dose)	CP-690,550 10 mg (single dose)
2	Day 1	Tac 5 mg q12h	CsA 200 mg q12h
	Day 2	Tac 5 mg q12h	CsA 200 mg q12h
	Day 3	Tac 5 mg q12h	CsA 200 mg q12h
	Day 4	Tac 5 mg q12h	CsA 200 mg q12h
	Day 5	Tac q12h[b]	CsA q12h[c]
	Day 6	Tac q12h	CsA (single dose) PLUS CP-690,550 10 mg (single dose)
	Day 7	Tac q12h	No treatment given (discharge)
	Day 8	Tac (single dose) PLUS CP-690,550 10 mg (single dose)	NA
	Day 9	No treatment given (discharge)	
Follow-up	Follow-up visit was 7 to 14 days after the last dose of CP-690,550		

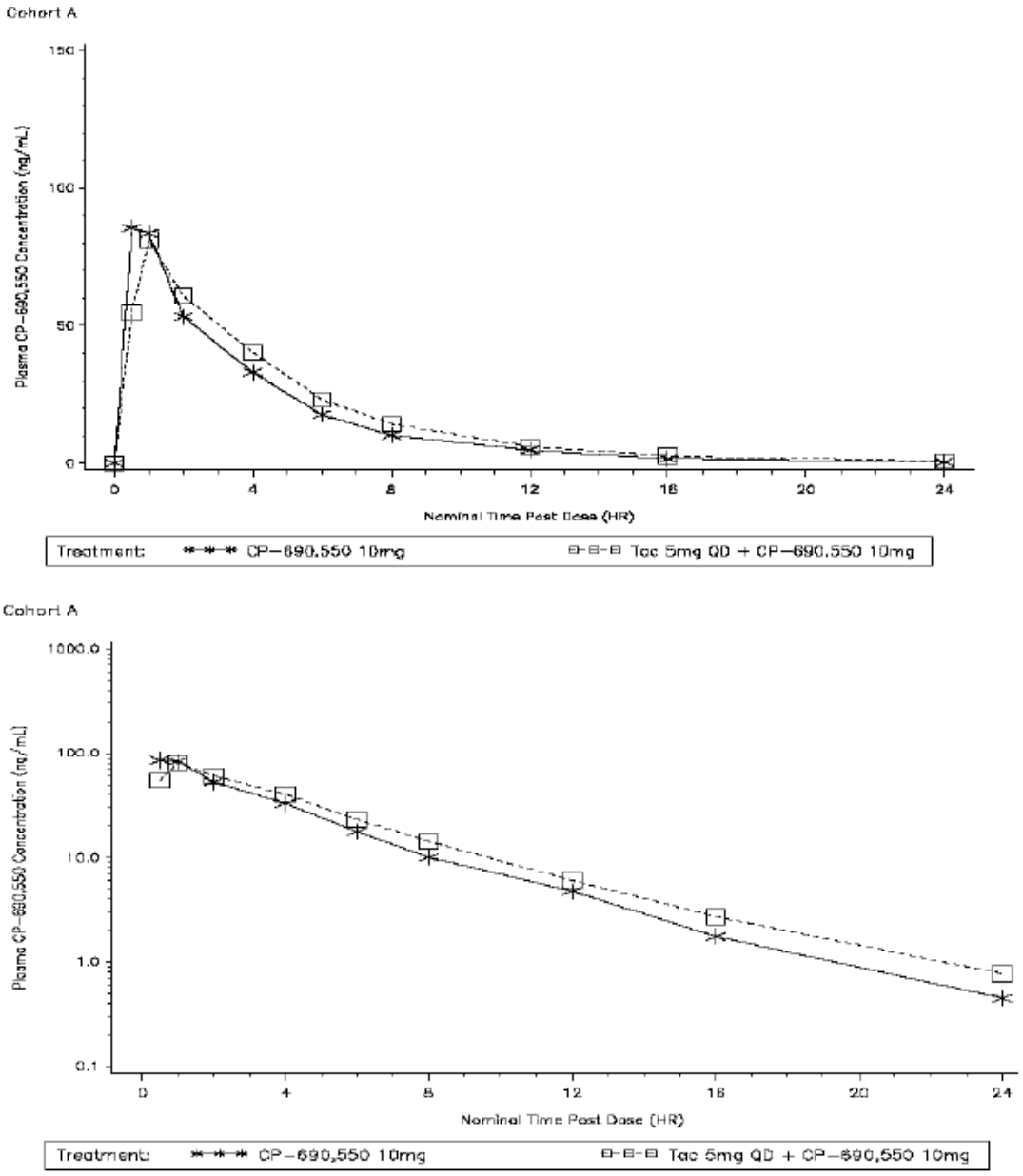
Source: Appendix A1

Abbreviations: BID = twice daily, CsA = cyclosporine, NA = not applicable, q12h = every 12 hours, Tac = tacrolimus

[a] Day was relative to the first day of dosing for each period. Day 1 of Period 2 was the same day as Day 2 of Period 1.

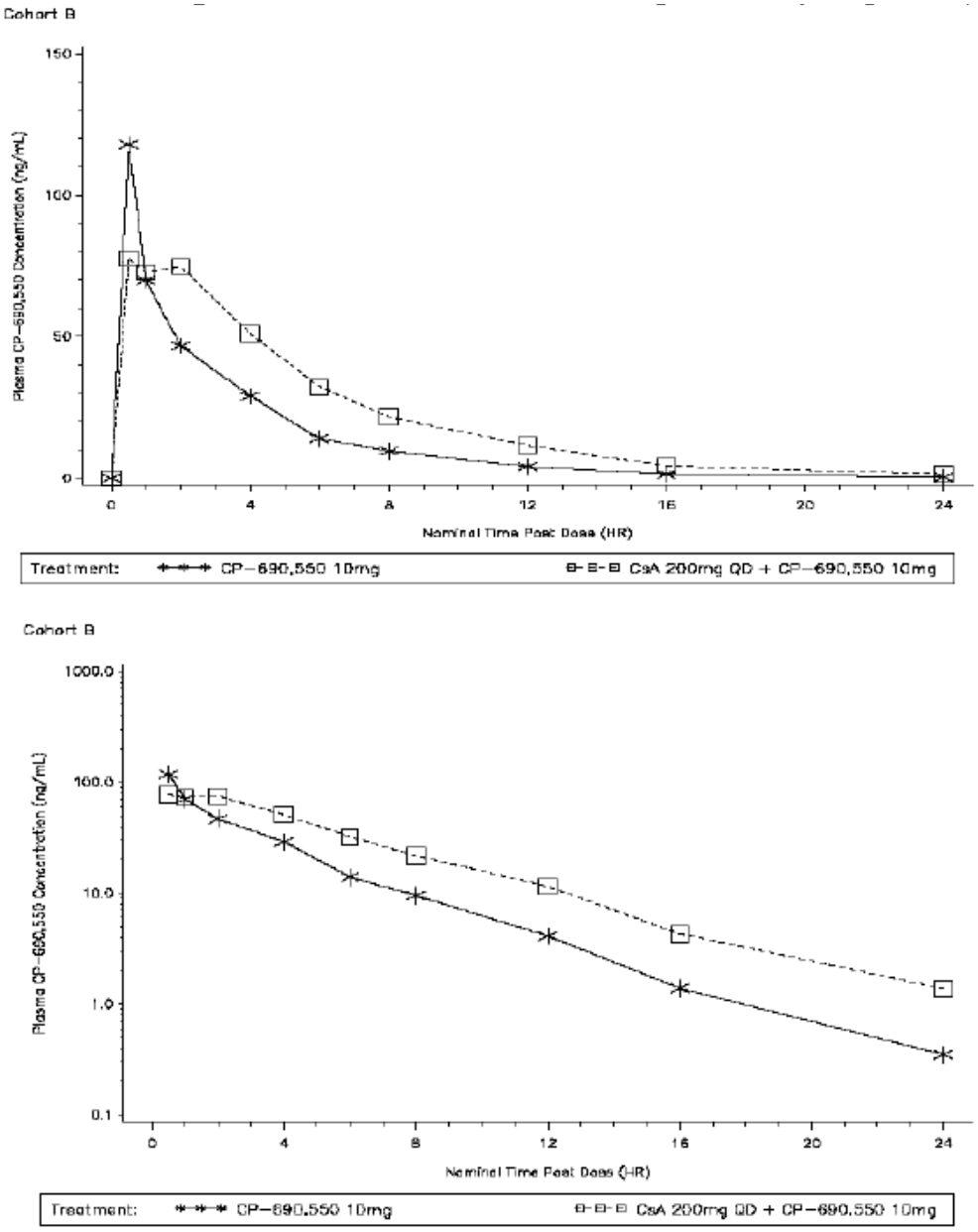
[b] The planned Tac dose was 5 mg BID.

[c] The planned CsA dose was 200 mg BID.



Source: Figures 14.1.1.1 and 14.1.1.2
Abbreviations: HR = hour, q12h = every 12 hours, QD = every day, Tac = tacrolimus
Upper and lower panels are linear and semi-logarithmic scales, respectively. Note that "QD" dosing in the legend for Tac describes the single morning dose on Day 8; Tac dosing was q12h on Days 1 through 7.

Figure 68: Median plasma CP-690,550 concentration - time profiles following single 10 mg oral dose alone and with multiple dose tacrolimus



Source: Figures 14.1.1.1 and 14.1.1.2
Abbreviations: CsA = cyclosporine, HR = hour, q12h = every 12 hours, QD = every day
Upper and lower panels are linear and semi-logarithmic scales, respectively. Note that "QD" dosing in the legend for CsA describes the single morning dose on Day 6; CsA dosing was q12h on Days 1 through 5.

Figure 69: Median plasma CP-690,550 concentration - time profiles following single 10 mg oral dose alone and with multiple dose cyclosporine

Table 66: Statistical summary of treatment comparison for CP-690,550 alone and with multiple dose Tac

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	CP-690,550 10 mg with Multiple-Dose Tac (Test)	CP-690,550 10 mg Alone (Reference)		
AUC_{inf} (ng*hr/mL)	410.59	338.99	121.12	113.24, 129.55
AUC_{last} (ng*hr/mL)	405.87	336.94	120.46	112.86, 128.57
C_{max} (ng/mL)	94.72	104.37	90.76	83.17, 99.03

Source: Table 13.5.3.1

Abbreviations: AUC_{inf} = area under the plasma concentration-time profile from time zero extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}), CI = confidence interval, C_{max} = maximum observed concentration within the dosing interval, Tac = tacrolimus

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

Table 67: Statistical summary of treatment comparison for CP-690,550 alone and with multiple dose CsA

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	CP-690,550 10 mg with Multiple-Dose CsA (Test)	CP-690,550 10 mg Alone (Reference)		
AUC_{inf} (ng*hr/mL)	533.21	307.98	173.13	161.79, 185.26
AUC_{last} (ng*hr/mL)	525.85	306.56	171.54	160.26, 183.60
C_{max} (ng/mL)	93.10	111.91	83.19	71.37, 96.96

Source: Table 13.5.3.2

Abbreviations: AUC_{inf} = area under the plasma concentration-time profile from time zero extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}), CI = confidence interval, C_{max} = maximum observed concentration within the dosing interval, CsA = cyclosporine

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

15. DDI with Midazolam

Trial # A3921059

Title: A Phase 1, Randomized, 2-Way Crossover, Multiple Dose, Open Label Study of the Effect of CP-690,550 on Midazolam Pharmacokinetics in Healthy Volunteers

- **Objective:**
  - To demonstrate the lack of effect of multiple-dose CP-690,550 on the pharmacokinetics (PK) of a single, oral dose of midazolam in healthy volunteers
- **Study design and treatment schedule:**
  - Randomized, 2-way crossover, multiple-dose, open-label study (see
  -
  -
  - **Table 68**).
- **PK Sampling Schedule**

  Midazolam PK blood samples were collected before dosing and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours postdose in Periods 1 and 2

Table 68: Treatment sequence for study A3921059

Sequence	Period 1	Washout Period	Period 2
Sequence 1 (N=12)	Treatment A	None	Treatment B
Sequence 2 (N=12)	Treatment B	Minimum of 7 days	Treatment A

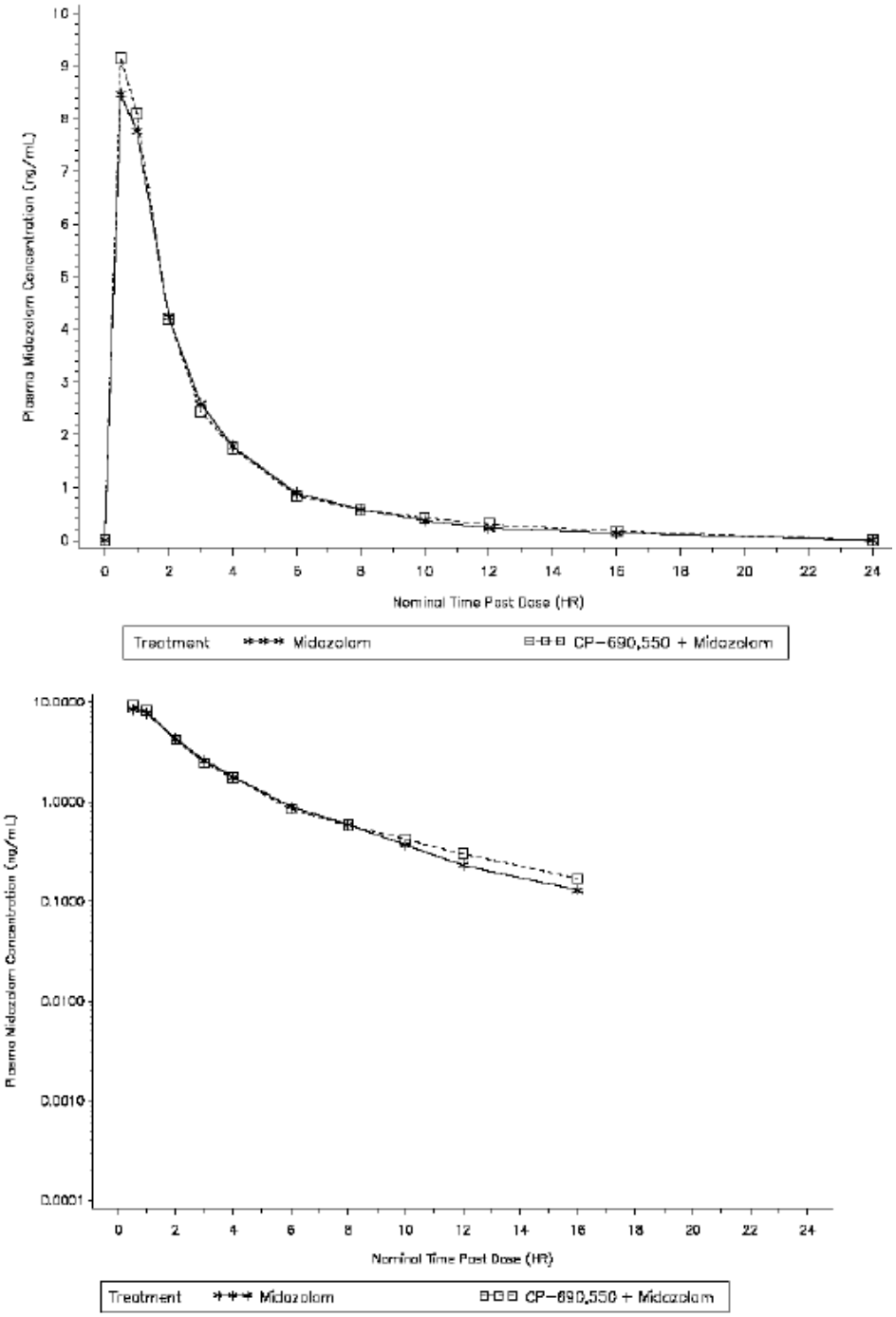
Source: Appendix A1
Abbreviations: BID = twice daily, PO = oral
Treatment A = single administration of midazolam 2 mg oral syrup. Treatment B = administration of 30 mg CP-690,550 PO BID for 6 days, followed by administration of a concurrent, single dose of midazolam 2 mg oral syrup on the morning of Day 7. Dosing with 30 mg CP-690,550 PO BID continued through the evening dose on Day 7.

- **Results**

There was no significant change in plasma concentration – time profiles of midazolam following administration with and without CP-690,550 (Figure 70). There was no statistical difference in AUC and Cmax parameters following coadministration of midazolam and CP-690,550 compared to midazolam alone (Table 69).

- **Conclusions**

There was no significant effect on PK of sensitive CYP3A4 substrate midazolam following coadministration with CP-690,550. Therefore, no dose adjustments are recommended for CYP3A4 substrates when coadministered with CP-690,550.



Source: Figures 14.1.1.1 and 14.1.1.2
Abbreviations: BID = twice daily, HR = hour
Upper and lower panels are linear and semi-logarithmic scales, respectively.

Figure 70: Median plasma midazolam concentration - time profiles following single 2 mg oral syrup dose alone and with multiple dose CP-690,550

Table 69: Statistical summary of treatment comparisons for midazolam single 2 mg oral syrup doses alone and with multiple-dose CP-690,550 (30 mg BID)

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Midazolam With CP-690,550 (Test)	Midazolam Alone (Reference)		
AUC_{inf} (ng*hr/mL)	26.81	25.79	103.97	95.57, 113.12
AUC_{last} (ng*hr/mL)	26.12	25.01	104.46	96.46, 113.13
C_{max} (ng/mL)	9.63	9.43	102.22	95.98, 108.87

Source: Table 13.5.3
Abbreviations: AUC_{inf} = area under the plasma concentration-time profile from time zero extrapolated to infinite time, AUC_{last} = area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last}), BID = twice daily, C_{max} = maximum observed concentration within the dosing interval, CI = confidence interval
[a] The ratios (and 90% CIs) are expressed as percentages

15. DDI with Oral Contraceptives

Trial # A3921071

Title: A Phase 1, Randomized, Open Label, 2-Way Crossover Study to Assess the Effect of Multiple Dose CP-690,550 on the Pharmacokinetics of Single Dose Oral Contraceptive (OC) Steroids in Healthy Female Subjects

- **Objective:**
  - To demonstrate the lack of effect of multiple oral doses of CP-690,550 on the PK of a single dose of a combination OC in healthy female subjects
- **Study design and treatment schedule:**
  - Randomized, 2-way crossover, open-label study evaluating effect of multiple doses of CP-690,550 on single-dose OC PK (see Table 70).
- **PK Sampling Schedule**

For treatment A, OC PK was assessed pre-dose and up to 48 hrs after dosing on day 1.
For treatment B, OC PK was assessed pre-dose and up to 48 hrs after dosing on day 10.

Table 70: Treatment sequence for study A3921071

Sequence	Period 1	Washout	Period 2
1. n = 10	Treatment A	None	Treatment B
2. n = 10	Treatment B	At least 10 days	Treatment A

Source: Section 16.1.1
Treatment A = single dose of oral contraceptive in the form of 1 Microgynon 30 oral tablet, containing 30 mcg of ethinyloestradiol and 150 mcg of levonorgestrel.
Treatment B = single dose of combination oral contraceptive in the form of 1 Microgynon 30 oral tablet, containing 30 mcg of ethinyloestradiol and 150 mcg of levonorgestrel on the morning of Day 10 following 9 days of CP-690,550 dosed at 30 mg orally twice daily.
Dosing with CP-690,550 at 30 mg orally twice daily continued through the evening dose on Day 11.

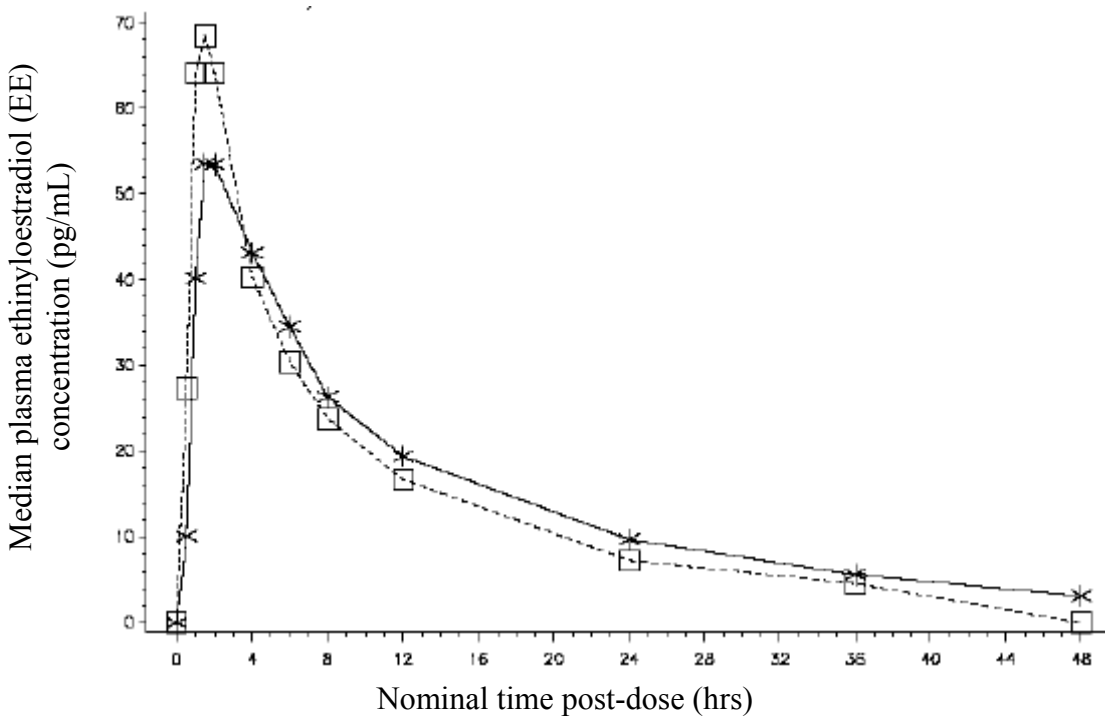
- **Results**

There was no significant change in plasma concentration – time profiles of ethinyloestradiol and levonorgestrel following administration with and without CP-690,550 (Figure 71 and Figure 72). There was no statistical difference in AUC and Cmax

parameters for OC following administration with and without CP-690,550 (Table 71 and Table 72).

- **Conclusions**

No dose adjustment recommended for coadministration of OC with CP-690,550.



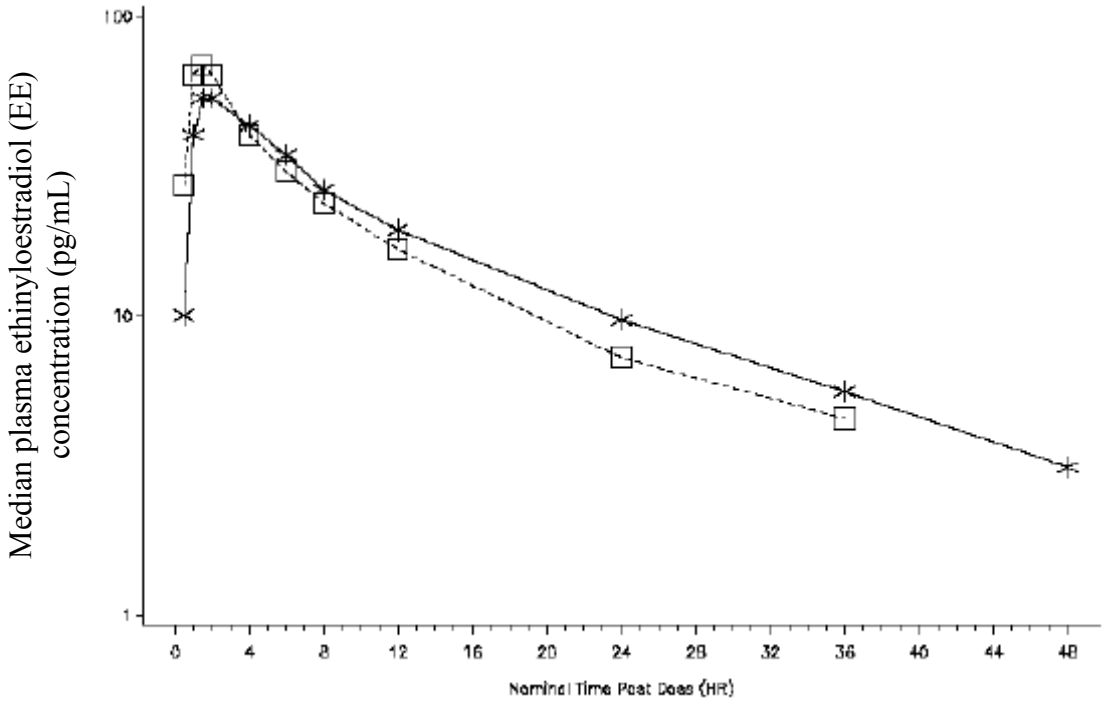


Figure 71: Median plasma ethinyloestradiol concentration - time profiles following single oral microgynon 30 dose alone and with multiple dose CP-690,550

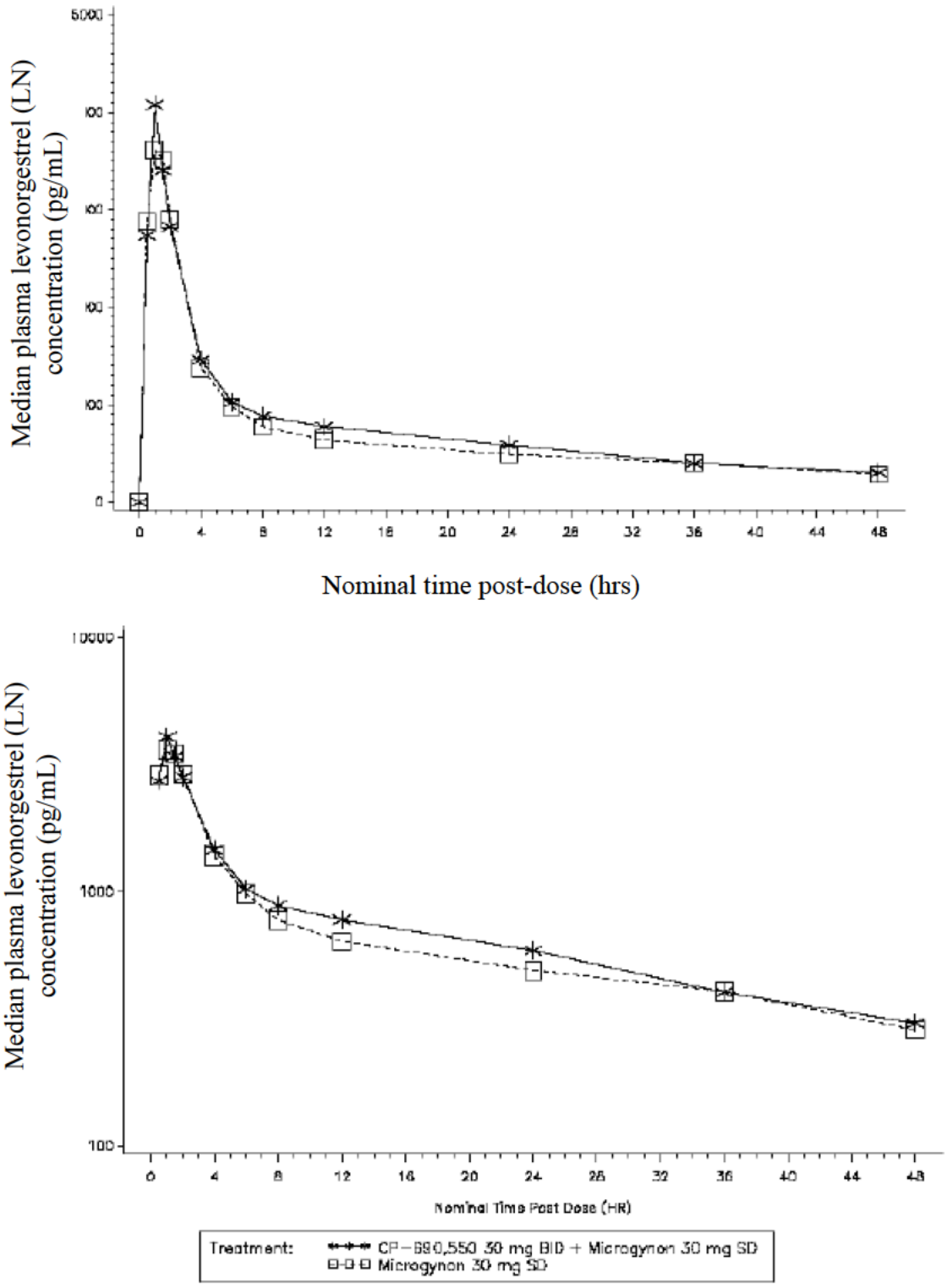


Figure 72: Median plasma levonorgestrel concentration - time profiles following single oral microgynon 30 dose alone and with multiple dose CP-690,550

Table 71: Statistical summary of treatment comparisons for plasma ethinyloestradiol following single oral microgynon 30 dose alone and with multiple-dose CP-690,550

Ethinyloestradiol Parameter (units)	Adjusted Geometric Means: Microgynon 30 With CP-690,550 (Test)	Adjusted Geometric Means: Microgynon 30 Alone (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
AUC_{inf} (pg.hr/mL)	762.8	715.9	106.55	98.91, 114.78
AUC_{last} (pg.hr/mL)	691.4	647.3	106.81	98.30, 116.06
C_{max} (pg/mL)	61.51	68.64	89.62	81.98, 97.97

Source: Table 14.4.3.3.1
Parameters are defined in Table 5.
CI = confidence interval.
[a] The ratios (and 90% CIs) are expressed as percentages.

Table 72: Statistical summary of treatment comparisons for plasma levonorgestrel following single oral microgynon 30 dose alone and with multiple-dose CP-690,550

Levonorgestrel Parameter (units)	Adjusted Geometric Means: Microgynon 30 With CP-690,550 (Test)	Adjusted Geometric Means: Microgynon 30 Alone (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
AUC_{inf} (pg.hr/mL)	45000	44610	100.87	94.73, 107.42
AUC_{last} (pg.hr/mL)	36580	34970	104.60	96.63, 113.22
C_{max} (pg/mL)	4242	3781	112.19	105.30, 119.53

Source: Table 14.4.3.3.2
Parameters are defined in Table 5.
CI = confidence interval.
[a] The ratios (and 90% CIs) are expressed as percentages.

BIOPHARMACEUTICS

15. Absolute Bioavailability

Trial # A3921077

Title: A Phase 1, Open Label, Single Dose, Randomized, Cross Over Study to Estimate the Absolute Oral Bioavailability of CP-690,550 in Healthy Subjects

- **Objective:**
  - To estimate the absolute bioavailability of a 10 mg oral dose of CP-690,550 compared to a 10 mg IV dose of CP-690,550.
- **Study design and treatment schedule:**
  - Randomized, 2-way crossover, single-dose, open-label study (Table 73)
- **PK Sampling Schedule**
  - PK samples were drawn up to 24 hrs in both sequence 1 and 2

Table 73: Treatment sequences for study A3921077

Sequence	Period 1	Washout	Period 2
1. (n= 6)	Treatment A	72 hours	Treatment B
2. (n= 6)	Treatment B	72 hours	Treatment A

Source: Section 16.1.1
Treatment A = single-dose of CP-690,550 (10 mg) in the form of an oral tablet.
Treatment B = single-dose of CP-690,550 (10 mg) in the form of a 30-minute intravenous infusion.

- **Results and Conclusions**

There absolute bioavailability of CP-690,550 following oral administration was 74%.

Table 74: Statistical summary for comparison of PK parameters following oral and intravenous administration

Parameter (units)	Adjusted Geometric Means: 10 mg Oral Tablet (Test)	Adjusted Geometric Means: 10 mg IV Infusion (Reference)	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
AUC_{inf} (ng.hr/mL)	299.7	404.2	74.14	70.32, 78.16
AUC_{inf}(dn) (ng.hr/mL/mg)	29.97	40.48[b]	74.03	70.21, 78.05
AUC_{last} (ng.hr/mL)	297.6	402.0	74.04	70.26, 78.03

Source: Table 14.4.3.3
CI=confidence interval
Parameters are defined in Table 5.
[a] The ratios (and 90% CIs) are expressed as percentages.
[b] Dose-normalized AUC_{inf} reflects a 2% lower IV dose (9.8 mg) for Subject 10011004.

16. Preliminary Relative Bioavailability and Food Effect

Trial # A3921005

Title: A Phase 1, Open-Label, Randomized, Crossover Study to Evaluate the Relative Bioavailability of CP-690,550 Tablets and Oral Powder for Constitution (OPC) and Effect of Food on the Pharmacokinetics of CP-690,550 Tablets

- **Objectives**
  - To evaluate the relative bioavailability of a single oral dose of the CP-690,550 tablets and the oral powder for constitution (OPC) under fasting conditions in healthy subjects
  - To evaluate the effect of food on the pharmacokinetics of a single oral dose of CP-690,550 tablets in healthy subjects
- **Study design and treatment schedule:**
  Randomized, open-label, 6-sequence, 3-period, crossover study with 3 treatments (Table 75). Treatment periods were separated by a washout period of at least 7 days.

Table 75: Dosing sequences in study A3921005

Sequence	Treatment Period 1	2	3
1	A	C	B
2	B	A	C
3	C	B	A
4	B	C	A
5	C	A	B
6	A	B	C

A=50 mg CP-690,550 tablet under fasting conditions.
B=50 mg CP-690,550 tablet under fed conditions.
C=50 mg CP-690,550 OPC under fasting conditions.

- **PK Sampling Schedule**

In each period PK samples were drawn at 0, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 16, and 24 hours after dosing

- **Results and Conclusions**

The tablet formulation and OPC had similar AUC under fasting conditions, but C_{max} for tablet formulation was 24% lower than OPC (Table 76). Food had no significant effect on AUC of tablet formulation but C_{max} was reduced by 26% (Table 77).

Table 76: Relative bioavailability of CP-690,550 given as 50 mg OPC or 50 mg tablets to healthy subjects under fasting conditions

	Arithmetic Mean (SD)		Adjusted Geometric Mean[b]		Comparison	
Parameter	Tablet - Fasting Test	OPC - Fasting Reference	Tablet - Fasting Test	OPC - Fasting Reference	Ratio (%) T/R	95% CI (%) Lower, Upper
AUC_{0-inf} (ng·h/mL)	1420 (367)	1460 (323)	1373.84	1426.37	96.32	91.52, 101.36
C_{max} (ng/mL)	363 (71.3)	479 (115)	356.07	465.98	76.41	68.67, 85.03
T_{max} (h)	1 (0.5-2)[a]	0.5 (0.25–0.5)[a]	--	--	--	--

[a] T_{max} median (range).
[b] Adjusted geometric mean based on linear model.

Table 77: Food effect PK parameters of CP-690,550 given as 50 mg tablets to healthy subjects

	Arithmetic Mean (SD)		Adjusted Geometric Mean[b]		Comparison	
Parameter	Tablet - Fed Test	Tablet - Fasting Reference	Tablet - Fed Test	Tablet - Fasting Reference	Ratio (%) T/R	95% CI (%) Lower, Upper
AUC_{0-inf} (ng·h/mL)	1620 (357)	1420 (367)	1579.30	1373.84	114.96	109.23, 120.98
C_{max} (ng/mL)	272 (63.9)	363 (71.3)	264.38	356.07	74.25	66.72, 82.63
T_{max} (h)	2 (0.5–4)[a]	1 (0.5-2)[a]	--	--	--	--

[a] T_{max} median (range).
[b] Adjusted geometric mean based on linear model.

17. Food Effect on Final Formulation

Trial # A3921076

Title: A Phase 1, Randomized, 2-Period, 2-Sequence, Open Label, Single Dose, Cross-Over Study to Evaluate the Effect of Food on Pharmacokinetics of Tasocitinib (CP-690,550) Tablets in Healthy Subjects

- **Objective**
  - To evaluate the effect of food on the PK of single 10 mg CP-690,550 commercial image tablet.
- **Study design and treatment schedule:**
  Randomized, open-label, single-dose, 2-way crossover study (Table 78)

Table 78: Treatment sequences for study A3921076

Sequence	Period 1	Washout	Period 2
1. (n = 8)	Treatment A	72 hours	Treatment B
2. (n = 8)	Treatment B	72 hours	Treatment A

Source: Section 16.1.1
Treatment A: Single dose of CP-690,550 10 mg under fed conditions.
Treatment B: Single dose of CP-690,550 10 mg under fasted conditions.

- **PK Sampling Schedule**

In each period PK samples were drawn at 0, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 16, and 24 hours after dosing

- **Results and Conclusions**

For the tablet formulation used in this study, food had no significant effect on AUC but decreased the C_{max} by 32% and median t_{max} increased from 0.5 to 2 hours (Table 79 and Table 80).

Table 79: Summary of plasma CP-690,550 PK parameter values following single oral doses

Pharmacokinetic Parameter [a], Units	CP-690,550 10 mg fed SD	CP-690,550 10 mg fasted SD
N	16	16
AUC_{inf} (ng*hr/mL)	285.7 (20)	269.5 (20)
AUC_{last} (ng*hr/mL)	284.1 (20)	268.4 (20)
C_{max} (ng/mL)	63.10 (32)	92.55 (26)
T_{max} (hr)	2.00 (0.500-4.00)	0.500 (0.483-2.00)
$t_{½}$ (hr)	3.118 (8)	3.068 (10)

Source: Table 14.4.3.1
Pharmacokinetic parameters are defined in Table 4.
CV = coefficient of variation; N = Number of subjects in the treatment group; SD = single dose.
[a] Geometric mean (%CV) for all except: median (range) for T_{max}; arithmetic mean (%CV) for $t_{½}$.

Table 80: Statistical summary of treatment comparison under fed and fasted conditions

Pharmacokinetic Parameter, Units	Adjusted Geometric Means: Test (CP-690,550 10 mg Fed SD)	Adjusted Geometric Means: Reference (CP-690,550 10 mg Fasted SD)	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
AUC_{inf} (ng*hr/mL)	285.7	269.5	106.03	(102.62, 109.56)
AUC_{last} (ng*hr/mL)	284.1	268.4	105.87	(102.44, 109.41)
C_{max} (ng/mL)	63.10	92.55	68.18	(58.39, 79.61)

Source: Table 14.4.3.3
Pharmacokinetic parameters are defined in Table 4.
CI = confidence interval; SD = single dose.
[a] The ratios (and 90% CIs) are expressed as percentages.

18. Pivotal Bioequivalence

Trial # A3921075

Title: Phase 1, Open-Label, Randomized, Single Dose, 3-Treatment, 3-Period, Cross-Over, Bioequivalence Study Comparing Phase 2B, Phase 3 and Commercial Image Tablet Formulations of Tasocitinib (CP-690,550) under Fasted Conditions

- **Objectives**
  - To determine the bioequivalence of commercial image tablet to Phase 3 tablet under fasting conditions
  - To determine the bioequivalence of commercial image tablet to Phase 2B tablet under fasting conditions
- **Study design and treatment schedule:**

Randomized, 3-way cross-over, single-dose, open-label study in which subjects were randomized to one of the six sequences (Table 81)

Table 81: Treatment sequences for study A3921075

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

Source: Section 16.1.1
Treatment A: Single oral dose of 10 mg CP-690,550 as commercial image tablet formulation.
Treatment B: Single oral dose of 10 mg CP-690,550 administered as two 5 mg Phase 3 tablets.
Treatment C: Single oral dose of 10 mg CP-690,550 administered as two 5 mg Phase 2B tablets.
n = number of subjects in subgroup.

- **PK Sampling Schedule**

In each period PK samples were drawn at 0, 0.25, 0.5, 1, 2, 4, 8, 12, 16, and 24 hours after dosing

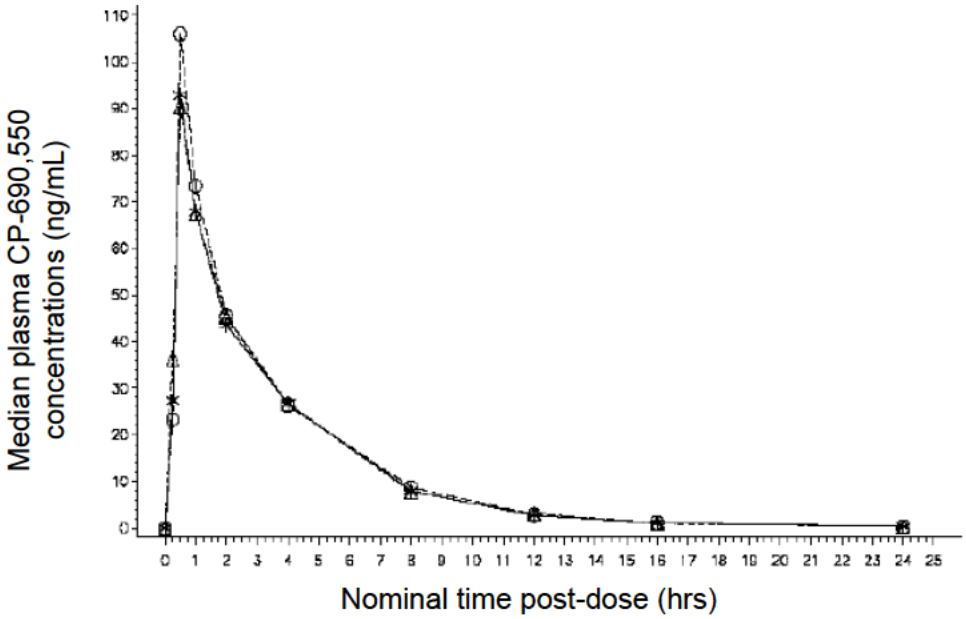
- **Results**

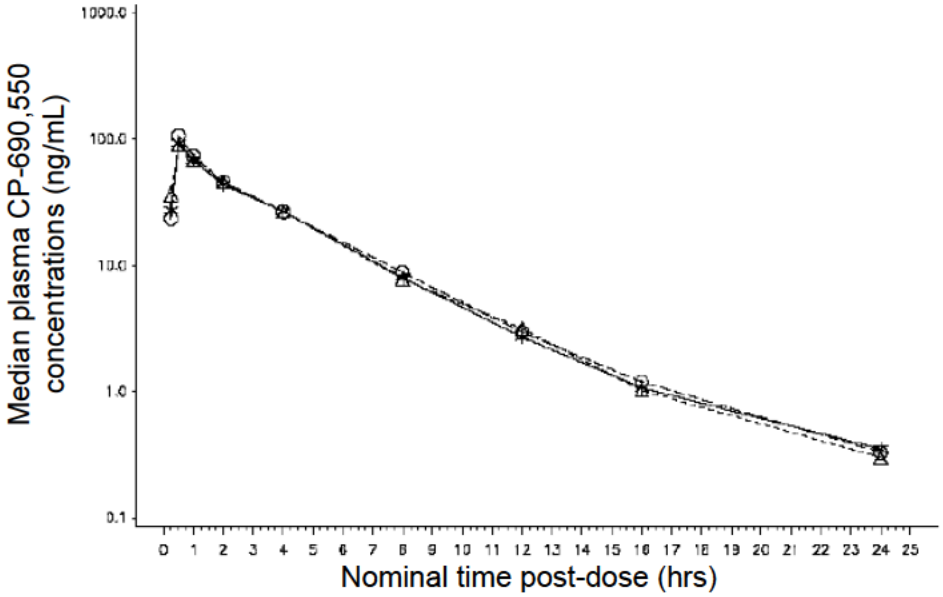
CP-690,550 plasma concentration – time profiles for all three dosage forms were almost

superimposable (Figure 73). Geometric mean ratios and 90% CI for comparison of PK parameters between formulations are all within 80 and 125 (Table 82), suggesting that these three formulations are bioequivalent.

- **Conclusions**

Tofacitinib tablet formulations used during Phase 2B and Phase 3 clinical investigation are bioequivalent with the commercial formulation.





Treatment
10 mg CP-690,550 Commercial image tablet formulation
10 mg (2 x 5 mg) CP-690,550 Phase 3 tablets
10 mg (2 x 5 mg) CP-690,550 Phase 2B tablets

Upper and lower panels are linear and semi-logarithmic scales, respectively

Figure 73: Median plasma concentration - time profiles following single 10 mg oral tablet doses

Table 82: Statistical summary of treatment comparisons for plasma CP-690,550 parameters following single 10 mg oral tablet doses

Parameter (Units)	Adjusted Geometric Means: Test	Adjusted Geometric Means: Reference	Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
1 x 10 mg Commercial Image tablet (test) versus 2 x 5 mg Phase 3 tablets (reference)				
AUC_{inf} (ng.hr/mL)	277.0	278.3	99.54	96.69, 102.47
AUC_{last} (ng.hr/mL)	275.5	276.8	99.52	96.68, 102.45
C_{max} (ng/mL)	96.46	91.69	105.20	95.57, 115.80
1 x 10 mg Commercial Image tablet (test) versus 2 x 5 mg Phase 2B tablets (reference)				
AUC_{inf} (ng.hr/mL)	277.0	279.9	98.97	96.13, 101.88
AUC_{last} (ng.hr/mL)	275.5	278.3	98.98	96.15, 101.89
C_{max} (ng/mL)	96.46	102.7	93.88	85.31, 103.32
2 x 5 mg Phase 3 tablets (test) versus 2 x 5 mg Phase 2B tablets (reference)				
AUC_{inf} (ng.hr/mL)	278.3	279.9	99.43	96.62, 102.31
AUC_{last} (ng.hr/mL)	276.8	278.3	99.45	96.65, 102.34
C_{max} (ng/mL)	91.69	102.7	89.24	81.20, 98.08

Source: Table 14.4.4.1
Parameters are defined in Table 4.
CI = confidence interval.
[a] The ratios (and 90% CIs) are expressed as percentages.

PK IN JAPANESE AND CHINESE SUBJECTS

19. PK in Japanese and Western Subjects

Trial # A3921036

Title: A Phase 1, Randomized, Subject- and Investigator-Blind, Sponsor-Open, Placebo-Controlled, Single- and Multiple-Dose Escalation Study to Investigate the Pharmacokinetics, Safety and Tolerability of CP-690,550 in Healthy Japanese and Western Subjects

- **Objectives**
  - To compare the pharmacokinetics, safety and tolerability of escalating single oral doses of CP-690,550 in healthy adult Japanese to Western subjects
- **Study design and treatment schedule:**

Randomized, subject- and investigator-blind, sponsor-open, placebo-controlled, single- and multiple-dose escalation study (
Table **83**). In cohort A, Westerner and Japanese subjects received single oral doses of 1, 5, and 30 mg, each separated by 2-day washout period.

Table 83: Treatment cohorts in study A3921036

Cohort	Race	Treatment
A	Japanese	CP-690,550 1 mg, 5 mg and 30 mg Single Dose (6 subjects) or Placebo (2 subjects)
	Westerner	CP-690,550 1 mg, 5 mg and 30 mg Single Dose (6 subjects) or Placebo (2 subjects)
B	Japanese	CP-690,550 15 mg Single Dose and 15 mg Multiple Dose (6 subjects) or Placebo (2 subjects)

- **PK Sampling Schedule**

In cohort A, blood samples for PK analysis were collected at 0 hour and 0.25, 0.5, 1, 2, 4, 8, 12, 16, 24 and 48 hours after dosing

- **Results**

CP-690,550 plasma concentration – time profiles between Western and Japanese subjects are comparable at all three studied dose levels, 1mg, 5mg, and 30 mg (Figure 74). The geometric mean ratios for comparison of PK parameters between two populations are close to 1 (Table 84), suggesting that PK parameters are comparable.

The PK profile in Japanese subjects after single and multiple dose were also comparable (Figure 75) with observed accumulation ratio of 1.15 (range: 0.997 to 1.31), which is approximately similar to the accumulation ratio observed in multiple dose study A3921003 (Table 47).

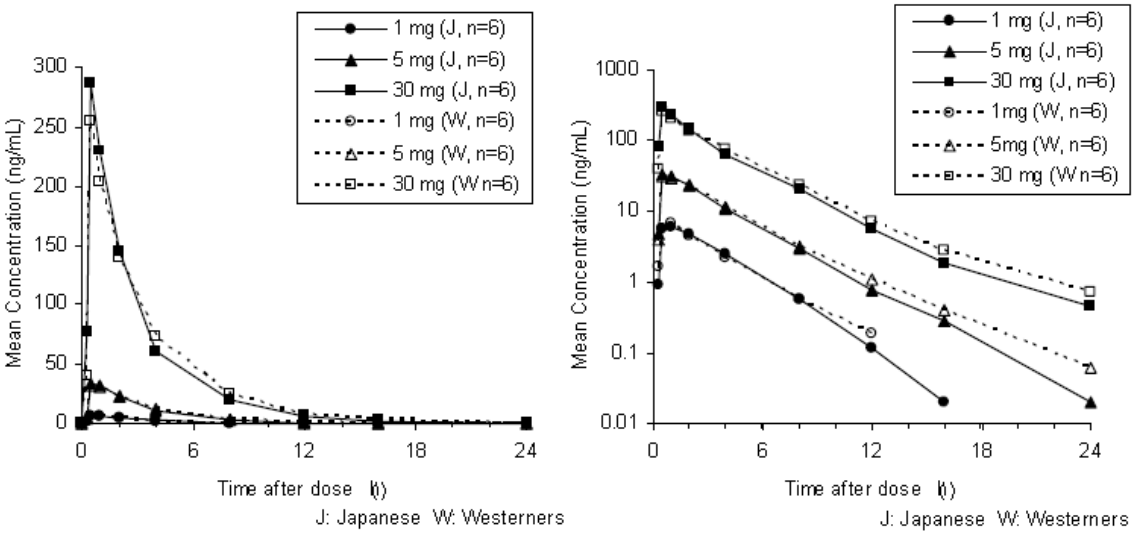
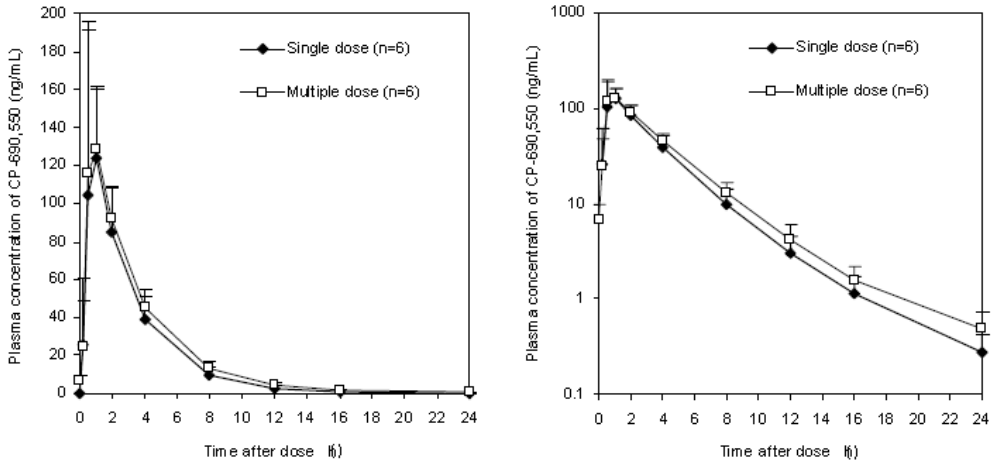


Figure 74: Mean plasma concentration of CP-690,550 following single oral dose administration in healthy Japanese and Western subjects

Table 84: Mean PK parameters of CP-690,550 following administration of single doses in healthy Japanese and Western subjects

		Japanese			Westerners		
		1 mg	5 mg	30 mg	1 mg	5 mg	30 mg
	n	6	6	6	6	6	6
C_{max} (ng/mL)	Geometric Mean	7.32	41.3	315	7.36	34.9	265
	%CV	14	35	25	22	27	18
	J/W (%)[a]	99.5	118	119	na	na	na
	90%CI	(81.1, 122)	(87.4, 161)	(93.0, 151)	na	na	na
AUC_{inf} (ng·h/mL)	Geometric Mean	22.0	111	754	22.8	119	788
	%CV	28	22	26	11	14	16
	J/W (%)[a]	96.6	93.5	95.6	na	na	na
	90%CI	(76.7, 122)	(76.3, 114)	(76.1, 120)	na	na	na
T_{max} (h)	Median	0.75	0.50	0.50	0.75	0.50	0.50
	Range	0.50-2.00	0.50-1.00	0.50-1.00	0.50-1.00	0.50-2.00	0.50-1.00
	J-W[b]	0.00	0.00	0.00	na	na	na
$t_{½}$ (h)	Arithmetic Mean	1.96	2.49	3.14	2.14	2.85	3.50
	Range	1.69-2.40	2.06-3.60	2.56-3.79	1.80-2.34	2.13-3.93	2.89-3.81
	J-W[b]	-0.19	-0.36	-0.36	na	na	na

Source: Tables 13.5.2.1 and 13.5.3
Abbreviation: CI = confidence interval; J = Japanese; na = not applicable; W = Westerner
[a] Ratio of Geometric Mean (Japanese / Westerners).
[b] Difference of Median or Arithmetic Mean (Japanese -Westerners).



Source: Tables 13.5.1.1.2 and 13.5.1.2

Figure 75: Mean (+SD) plasma concentration of CP-690,550 following administration of a singe oral dose of 15 mg and multiple oral doses of 15 mg BID for 5 days in Japanese healthy subjects

- **Conclusions**

The PK of tofacitinib is comparable between subjects with Japanese and Western ethnicity.

20. PK in Chinese Subjects

Trial # A3921065

Title: An Open Label, Single and Multiple Dose Study to Investigate the PK, Safety and

Tolerability of CP-690,550 in Healthy Chinese Subjects

- **Objective**
  - To characterize the PK of single and multiple oral doses of CP-690,550 in healthy adult Chinese subjects
- **Study design and treatment schedule:**

Open-label, single- and multiple-dose PK study in healthy adult male and female Chinese subjects

Table 85: Dosing sequence for study A3921065

Study Day	Day 1	Day 2 to Day 5	Day 6
CP-690,550	2 x 5-mg tablets at 8:00 AM	2 x 5-mg tablets in the morning (approximately 8:00 AM) and in the evening (approximately 8:00 PM) with a dosing interval approximately 12 hours apart	2 x 5-mg tablets at approximately 8:00 AM

Source: 16.1.1

- **Results**

The PK characteristics of tofacitinib in Chinese subjects were similar to that observed in subjects from Western or Japanese ethnicities. These PK characteristics were: a rapid absorption with T_{max} of approximately 0.5 hrs, short elimination half-life of about 2.5-3.3 hrs, attainment of steady-state by 24 hours and negligible accumulation after multiple doses (Table 86).

Table 86: Summary of PK in Chinese subjects

	Summary Statistics[a] by Treatment	
CP-690,550 Parameter (Units)	**Day 1 (Single-Dose)**	**Day 6 (Multiple-Dose)**
N	12	12
AUC_{inf} (ng.hr/mL)	274.8 (13)	NA
AUC_{last} (ng.hr/mL)	273.8 (13)	NA
AUC_{tau} (ng.hr/mL)	265.4 (13)	275.0 (12)
C_{max} (ng/mL)	98.28 (40)	89.19 (33)
T_{max} (hr)	0.500 (0.250-2.00)	0.500 (0.250-2.00)
C_{min} (ng/mL)	NA	2.265 (38)
C_{trough} (ng/mL)	NA	4.688 (38)
$t_{½}$ (hr)	3.319 (12)	2.479 (11)
R_{ac}	NA	1.036 (10)

Source: Table 14.4.3

N = number of subjects in the treatment group; NA = not applicable; CV = coefficient of variation.

Parameters are defined in Table 5.

[a] Geometric mean (%CV) for all except: median (range) for T_{max}; arithmetic mean (%CV) for $t_{½}$

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06/25/2012

ONDQA BIOPHARMACEUTICS REVIEW

Original NDA#:	**203-214 (000)**
Submission Date:	10/21/2011, 4/30/2012, 6/8/2012, 6/15/2012
Brand Name:	(b) (4)® Tablets
Generic Name:	Tofacitinib Citrate
Formulation:	Tablets
Strength:	5 and 10 mg
Applicant:	Pfizer
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

SYNOPSIS:

Submission: Tofacitinib is an inhibitor of the Janus Kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. The oral tablet formulation of Tofacitinib, dosed as 5 mg or 10 mg twice a day, is being developed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease modifying antirheumatic drugs. The current NDA is a QbD submission, which is involved in a pilot program of parallel review with European Medicines Agency (EMA).

Review: The Biopharmaceutics review is focused on (b) (4) the setting of the acceptance criterion for the disintegration test.

COMMENTS:

1. From the Biopharmaceutics perspective the commercial 5 mg and 10 mg strengths can be considered similar based on the following observations.
   - The formulations of the 5 mg and 10 mg commercial tablets (b) (4) (b) (4)
   - The two strengths share the same manufacturing process.
   - Both, the 5 mg and the 10 mg tablets dissolve rapidly (b) (4) in 15 minutes using mild conditions, such as basket at 100 rpm in 0.1N HCl).
2. The Applicant's proposal of using the disintegration test in lieu of the dissolution test is acceptable.
3. (b) (4) The Applicant already agreed to keep the disintegration test in the drug product's specifications table for release and stability.
4. The applicant's proposal of setting the acceptance criterion of (b) (4) for the disintegration test is acceptable.

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 203-214 for (b) (4)® (tofacitinib citrate) Tablets is recommended for approval.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes, Ph.D. Date
ONDQA Biopharmaceutics Team Leader

cc: NDA 203-214 *Darrts*

APPENDIX I - SUMMARY OF REGULATORY ISSUES

There are four biopharmaceutics related issues, which are listed below.

1. The linkage between the clinical and to-be-marketed formulations

The Phase III formulation and the to-be-marketed formulation are different in the composition. In addition, the Phase III studies used only the 5 mg tablets, while the to-be-marketed formulations include the 5 mg and 10 mg tablets. The NDA submission includes a pivotal bioequivalence (BE) study (Study A3921075) supporting the linkage among the Phase 2B, Phase 3, and the to-be-marketed commercial tablets. OCP is evaluating this bridging BE study and will provide a recommendation regarding its acceptability.

From the Biopharmaceutics perspective, the commercial 5 mg and 10 mg strengths can be considered similar based on the following observations.

- The formulations of the 5 mg and 10 mg commercial tablets (b) (4)
- The two strengths share the same manufacturing process.
- Both, the 5 mg and the 10 mg tablets dissolve rapidly (b) (4) in 15 minutes using mild conditions, such as basket at 100 rpm in 0.1N HCl).

Therefore, the link between the clinical and the to-be-marketed formulations is established, provided the BE study is considered to be adequate.

2. Substitution of dissolution test with disintegration test.

The Applicant's proposal for using the disintegration test in lieu of the dissolution test is acceptable due to the following reasons:

- Tofacitinib is classified as a BCS Class-III drug substance with a high solubility.
- The drug product showed fast dissolution characteristics supported by the dissolution profiles obtained in different pH media, apparatus and agitation speeds, including Apparatus I at 100 rpm, Apparatus II at 50 rpm, 75 rpm, media of pH 1.2 (0.1 N HCl), pH 4.5 and pH 6.8.
- The dissolution profile of the aberrant formulations is similar to the to-be-marketed formulation. The aberrant formulations included changes in the (b) (4)
- The disintegration method showed to be more discriminating than the dissolution method. These findings are supported by the investigation of the relationship between dissolution and disintegration and the evaluation of the ability of each

method to discriminate against deviations in formulation or manufacturing conditions using aberrant formulations.

- Dissolution does not change with storage time. There were no trends observed in the dissolution values at 15 minutes for samples stored under long term stability conditions at 25°C/60% RH and 30°C/75% RH for 12 months, and under accelerated conditions at 40°C/75% RH for 6 months.

3. Setting the acceptance criterion for the disintegration test

Based on the provided data the acceptance criterion for the disintegration test should be set at (b) (4), due to the following reasons:

- The maximum disintegration time in all the studies, including DOE and the study using aberrant tablets, is (b) (4).
- The relationship between dissolution and disintegration time beyond (b) (4) is not clear.
- One of the advantages of using the disintegration method is that it is more discriminating than the dissolution method. Inadequate control of disintegration test will lose this advantage.
- The stability batches showed less than (b) (4) disintegration time under various conditions up to 12 months as shown in the following figures.

(b) (4)

Batch-Strength-Container-Condi ion

Disintegration Time for Stability Batches after 3 Months

(b) (4)

Batch-Strength-Container-Condi ion

Disintegration Time for Stability Batches after 6 Months

(b) (4)

Batch-Strength-Container-Condi ion

Disintegration Time for Stability Batches after 9 Months

(b) (4)

Batch-Strength-Container-Condi ion

(b) (4)

Batch-Strength-Container-Condi ion

It is recommended that the acceptance criterion of (b) (4) for the disintegration test be implemented and a revised specification table for their drug product be provided. This recommendation was conveyed to the Applicant*.

On 6/1/12, the Applicant provided additional information/data clarifying that all DOE and aberrant tablets data were generated on uncoated tablet cores as part of the process understanding studies. An acceptance criterion of (b) (4) was proposed for the disintegration test.

Based on the evaluation of these data and on the expected in vivo performance of the drug product, the Applicant's proposal is acceptable. All DOE and aberrant tablet studies showed rapid dissolution with a maximum disintegration time of (b) (4). However, all these studies were conducted using uncoated tablet cores and the disintegration times of the coated tablets are approximately (b) (4) higher than for the uncoated cores (see Appendix III). Therefore, an acceptance criterion of (b) (4) for disintegration testing is reasonable.

***Note**; There were several communications between FDA and Applicant addressing the disintegration acceptance criterion issue [i.e., **1)** FDA's IR Letters dated 3/16/12 and 6/1/12; **2)** a TCON held on 5/30/12; and **3)** Applicant's responses dated 4/30/12 and 6/1/12].*

(b) (4)

The Applicant agreed to keep the disintegration testing in the specifications of the drug product.

APPENDIX II - BIOPHARMACEUTICS EVALUATION

1. The Submission:

QTPP: The summary of the Quality Target Product Profile (QTPP), and the link to the quality attributes of the CP-690,550-10 tablets based on the Applicant are presented in the following table.

Quality Target Product Profile		Quality Attributes	
Product Attribute	**Target**	**Test Name**	**Acceptance Criteria**
Dosage Form	Immediate release tablets with film coating	Appearance (visual)	5mg: white, round, film coated tablet with Pfizer on one side and JKI 5 on the other side (b) (4)
Tablet Color	White (5 mg): (b) (4)		
Tablet Shape	Round		
Tablet Debossing	Appropriate markings to differentiate the dose		
Tablet Weight(s)	206 mg (5 mg) (b) (4)		
Mode of Administration	Oral - twice daily		
Identity	Positive for active ingredient	ID (LC)	Retention time of the main peak matches that of reference standard
		ID (NIR/UV and LC)	NIR: Positive identification UV & LC: Spectrum of the major peak matches that of the reference standard
Strength	5 mg and 10 mg	Assay (NIR/LC)	95.0-105.0% of Label Claim - EU 90.0-110.0% of Label Claim - US
Assay	Meet pharmacopeia requirements		
Degradants and Impurities	Meets criteria of ICH Q3B(R2)	Specified Degradants (LC)	(b) (4)
		Unspecified Degradants (LC):	
		Total Degradation (LC)	
Uniformity of Dose	Meets pharmacopoeia requirements	Uniformity of Dosage Units (NIR/LC)	Meets pharmacopoeia requirements
Drug Release	Rapid disintegration and dissolution	Disintegration	Within (b) (4)
Microbiological Limits	Meets pharmacopoeia requirements	Microbiological limits	Meets pharmacopoeia requirements
Intended Markets	US, EU, Japan, and others	Excipient CoA	Meets pharmacopoeia requirements
Formulation Ingredients	Acceptable for intended markets		
Shelf Life	Minimum 24 months	Registration Stability Testing	Meets specifications at the end of shelf life
		(b) (4)	
Packaging Materials	(b) (4) (b) (4) sealed HDPE bottle with desiccant	CoA Provided by Supplier	Conforms
Primary Packaging	(b) (4) bottles	Package Check	Conforms

As seen, rapid disintegration and fast dissolution were defined as QTPP for drug release, for which the quality attribute was disintegration time.

2. Physiochemical properties

The drug substance of tofacitinib is highly soluble as shown in the following table.

Aqueous Solubility of CP-690,550-10

Aqueous Solution pH	Solubility (mg/mL)
1.00	>28
2.34	7.69
3.90	3.48
4.53	0.59
5.17	0.27
6.35	0.12
6.36	0.13
>8	0.20
Unbuffered water (pH 3.54)	2.9

The permeability classification is based on data from the human oral bioavailability study (A3921077), the human ADME study (A3921010), in vitro Caco-2 permeability assessments and the rat single pass intestinal perfusion (SPIP) study.

The mean absolute oral bioavailability of the commercial CP-690,550-10 tablets (A3921077) was 74.14%, which is less than the 90% criterion described in the BCS guidance for a Class I drug substance.

In the human ADME study (A3921010), the mean total percentage of administered radioactive dose recovered was 93.9%, with 80.1% in the urine and 13.8% in the feces.

In vitro permeability assessments indicate that apparent permeability (Papp) values of CP-690,550 (free base) at concentrations 0.01×, 0.1× and 1× of clinical dose (5 mg in 250 mL) were lower than that of metoprolol (a highly permeable compound used as the reference).

Permeability of CP-690,550 was also determined using rat single pass intestinal perfusion (SPIP) system with metoprolol as the high permeability standard. Permeability coefficient (Peff) values of CP-690,550 at concentrations 0.1× and 1× of clinical dose (5 mg in 250 mL) were lower than that of metoprolol.

Based on these results, the Applicant classified the drug substance of tofacitinib CP-690,550-10 as a BCS III compound.

3. The compositions

The composition of 5 mg strength is shown in the following table.

Component	Function	Reference to Standard	Theoretical Unit and/or Formula
CP-690,550-10	Active	Pfizer	(b) (4)
Microcrystalline Cellulose[2]	(b) (4)	NF, Ph. Eur., JP	
Lactose Monohydrate		NF, Ph. Eur., JP	
Croscarmellose Sodium		NF, Ph. Eur., JP	
Magnesium Stearate		NF, Ph. Eur., JP	
(b) (4)		Pfizer	
		USP, Ph. Eur., JP	
Total Finished Tablet[5]			206.00 mg

Note: NF = National Formulary; USP = United States Pharmacopeia; Ph. Eur. = European Pharmacopeia; JP = Japanese Pharmacopeia

(b) (4)

(b) (4)

4. Dissolution Methodology

A validated dissolution method was used for CP-690,550-10 tablets and it is performed in accordance with the following dissolution testing conditions.

Apparatus:	Apparatus I (baskets)
Medium:	0.1N HCl
Volume:	900 mL
Agitation:	100 RPM
Analysis:	UV or HPLC

The dissolution conditions (medium, apparatus and agitation speed) were developed. The evaluation was performed on 12 units for each lot of tablets and these tablets were analyzed under several dissolution conditions. CP-690,550-10 tablets were found to exhibit fast release (b) (4) in 15 minutes) characteristics throughout the physiological pH range. The dissolution profiles were independent of the medium (0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer) and tablet strength (5 mg, 10 mg) in baskets at 100 RPM.

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(b) (4)

[redacted]

Through communication, the Applicant agreed to keep the disintegration test in the product specifications.

7. Studies bridging the to-be-marketed and the clinical formulations

The Phase III formulation and the to-be-marketed formulation are different in the composition. In addition, the Phase III studies used 5 mg tablets while the to-be-marketed formulations include 5 mg and 10 mg tablets. A pivotal bioequivalence (BE) study (Study A3921075) evaluated the BE between CP-690,550 Phase 2B, Phase 3, and the commercial tablets. This was a Phase 1, open-label, randomized, 6-sequence, 3-period, crossover study to determine the bioequivalence of Phase 2B, Phase 3 and commercial tablet formulations of CP-690,550 in healthy volunteers. Subjects were randomized to 1 of 6 treatment sequences as described in the following table.

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

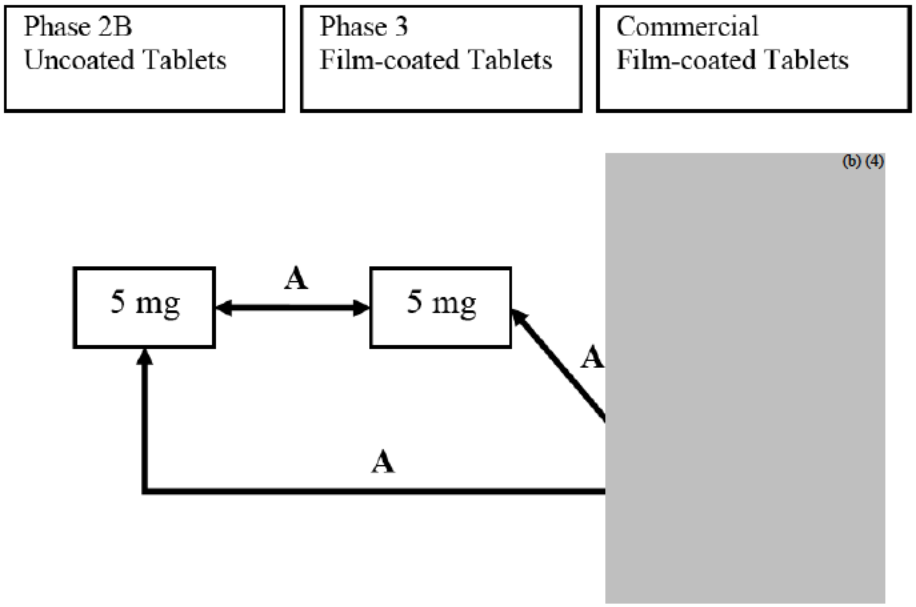
Source: CSR A3921075, Section 16.1.1
Treatment A: Single oral dose of 10 mg CP-690,550 as commercial tablet formulation.
Treatment B: Single oral dose of 10 mg CP-690,550 administered as two 5 mg Phase 3 tablets.
Treatment C: Single oral dose of 10 mg CP-690,550 administered as two 5 mg Phase 2B tablets.
n = number of subjects in subgroup.

A total of 26 male subjects were assigned to study treatment, with 24 subjects (4 per sequence) receiving all 3 treatments and completing the study. Two subjects discontinued

from the study. Following a 10-hour fast, CP-690,550 was administered to each subject during each treatment period.

In vitro dissolution and human BE data bridging the tablet formulations used in pivotal efficacy and safety trials (Phase 2B and Phase 3 studies of 5 and 10 mg twice-daily (BID) doses) with the commercial tablets are illustrated in the following Figure.

Figure. In vitro Dissolution and BE Data to Bridge CP-690,550 Phase 2B, Phase 3 and Commercial Tablets



A. Bridged by human BE study (Study A3921075)
B (b) (4) both tablets are rapidly dissolved (b) (4) dissolved in 15 minutes)

The pivotal BE study (A3921075) performed using the highest strength (10 mg) of the commercial tablet, showed that the Phase 2B, Phase 3 and commercial tablets are bioequivalent to each other*. The 5 mg (lowest strength) commercial tablet uses the (b) (4) same manufacturing process. As shown in the following table, both the 5 mg and the 10 mg tablets dissolve rapidly (b) (4) in 15 minutes using basket at 100 rpm in 0.1N HCl). Thus, the 5 and 10 mg strength commercial tablets can be considered to be bioequivalent.

Study No.	Product ID [Batch No.]	Dosage Form	Conditions	No. of Dosage Units	Mean % Dissolved (range) 15 min	30 min	45 min	60 min
A3921075	D0904982 [963918-3001]	10 mg Commercial	Apparatus: I (Baskets) Rotation Speed: 100 rpm Medium/Temperature: 0.1N HCl @ 37°C Medium Volume: 900 mL	6	97	98	98	98 (b) (4)
NA	D0904981 [963908-3000]	5 mg Commercial	Apparatus: I (Baskets) Rotation Speed: 100 rpm Medium/Temperature: 0.1N HCl @ 37°C Medium Volume: 900 mL	6	96	97	97	97 (b) (4)

NA – Not applicable; NT- Not tested

* BE study (A3921075) is being reviewed by OCP.

APPENDIX III

COMMUNICATION HISTORY BETWEEN FDA AND THE APPLICANT

1. The Agency issued an information request on 3/16/2012, including the following comment.

> Your proposal of using the disintegration test in lieu of the dissolution test is acceptable. (b) (4) [redacted]. Implement this criterion and provide a revised specification table for your drug product. (b) (4) [redacted] At the present time, in accordance with CFR, the disintegration test is required. However, if an acceptable alternate measure of bioavailability is provided, the (b) (4) [redacted]

The Applicant provided the following response on 4/30/2012.

> As per the Agency's request, Pfizer will keep disintegration as a performance test for the tofacitinib tablets.
>
> The disintegration test is used as a simple quality control check to ensure that immediate release tablets fully disperse upon contact with liquid media (rather than gradually eroding or swelling). Typically, immediate release tablets (such as the tofacitinib tablets) have in-vitro disintegration times in water of between 5 and 15 minutes. Lot-to-lot and sample-to-sample variation in disintegration testing results are typically of the order of several minutes.
>
> (b) (4) [redacted]

2. A teleconference was held on May 30, 2012, during which the Agency provided the bases for the recommended acceptance criterion for disintegration time. The Applicant clarified that all DOE and aberrant tablet data were generated on uncoated tablet cores.

3. The following comments regarding the acceptance criterion of disintegration were conveyed to the Applicant in an information request (IR) dated 6/1/2012.

> (b) (4) [redacted] Based on the information you provided, the disintegration time is less than (b) (4) [redacted] for all the DoE studies and even for the studies on the aberrant tablets. Therefore, an acceptance criterion

of less than (b) (4) should be implemented for the disintegration test of your product. Provide the revised specifications table for your drug product and update your application accordingly. However, if you do not agree with our recommendation, justify your proposal with adequate supportive data.

4. The Applicant submitted responses to the above IR on 6/8/2012, in which the following explanations were provided.

- All DOE and aberrant tablet data were generated on uncoated tablet cores as part of the process understanding studies. Data showed that the disintegration times of the coated tablets are approximately (b) (4) greater than for the uncoated cores as shown in the following table.

Lab Scale Development Batch Disintegration Data (Minute: Second)

(b) (4)

- For these studies average (mean) disintegration times were reported, in contrast to the maximum disintegration times that are reported for the release testing of the coated tablets.

The Applicant proposed an updated specification of NMT (b) (4) for the disintegration test used for the evaluation of this product.

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

/s/

JOHN Z DUAN
06/19/2012

ANGELICA DORANTES
06/19/2012

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	203214	Brand Name	TBD
OCP Division (I, II, III, IV, V)	II	Generic Name	Tofacitinib
Medical Division	Pulmonary, Allergy, and Rheumatology Products	Drug Class	JAK kinase inhibitor
OCP Reviewer	Lokesh Jain, Ph.D.	Indication(s)	Rheumatoid Arthritis
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Tablets
Pharmacometrics Reviewer	Lokesh Jain, Ph.D. & Atul Bhattaram, Ph.D.	Dosing Regimen	5 mg BID; some patients may benefit from 10 mg BID based on clinical response
Date of Submission	10/21/2010	Route of Administration	Oral
Estimated Due Date of OCP Review	06/26/2011	Sponsor	Pfizer, Inc.
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	07/21/2011		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	24		
I. Clinical Pharmacology				
Mass balance:	X	1		A3921010
Isozyme characterization:	X	4		DM2004-690550-046 DM2007-690550-067
Blood/plasma ratio:	X	1		CP-690550_18Feb11_055956
Plasma protein binding:	X	2		DM2001-690550-018 DM2002-690550-025
Transporter specificity:	X	6		XT088024/ (b) (4) (b) (4) 10/17Oct08/060532 CP-690550_15Oct10_175813 CP-690,550/09Jun08/135323 CP-690550_28Jul10_192119 CP-690550_02Aug10_095440
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	1		A3921002
multiple dose:	X	2		
Patients-				
single dose:	X			
multiple dose:	X	4		A3921003
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		

Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**5**		A3921054, A3921056, A3921020, A3921013, A3921014
In-vivo effects of primary drug:	**X**	**7**		A3921013, A3921071, A3921059
In-vitro:	**X**	**3**		DM2001-690550-020 DM2007-(b) (4)001
Subpopulation studies -				
ethnicity:	**X**	**3**		A3921036, A3921065
gender:				Population PK
pediatrics:				Requested waiver for age <2 years and submitted PPSR for age 2-18 years
geriatrics:				Population PK
renal impairment:	**X**	**1**		A3921004, A3921006, A3921033
hepatic impairment:	**X**	**1**		A3921015
PD -				
Phase 2:	**X**	**5**		A3921019, A3921035, A3921025, A3921039, A3921040
Phase 3:	**X**	**5**		A3921032, A3921044, A3921045, A3921046, A3921064
PK/PD -				
Phase 1 and/or 2, proof of concept:				A3921025, A3921035
Phase 3 clinical trial:				A3921064
Population Analyses -				
Data rich:	**X**	**12**		Population PK and PK-PD analysis with data from Phase 2 trials
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		A3921077
Relative bioavailability -				
solution as reference:	**X**	**1**		A3921005
alternate formulation as reference:	**X**	**1**		A3921075
Bioequivalence studies -				
traditional design; single / multi dose:				A3921075
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		A3921076
Bio-waiver request based on BCS				
BCS class	**X**			
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies	**X**	**1**		Thorough QTc study
Genotype/phenotype studies	**X**			A3921028 CYP2C19 genotyping
Chronopharmacokinetics				
Pediatric development plan	**X**			Submitted
Literature References				
Total Number of Studies		**80**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the	X			

	validity of the analytical assay?				
5	Has a rationale for dose selection been submitted?	X			Dose was selected based on results of trials 1218.25 and 1218.35
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	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)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	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?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_____Yes__

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
- None

Lokesh Jain	08/02/10
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni	08/02/10
Team Leader/Supervisor	Date

Submission in brief:

Indication and mechanism of action

Pfizer, Inc. has submitted the NDA 203214 seeking the marketing approval for Tofacitinib, to be used as monotherapy or in combination with methotrexate or other nonbiologic disease modifying anti-rheumatic drugs (DMARDs), for the treatment of patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more DMARDs. The recommended dose is 5 mg twice-daily (BID) with an increase to 10 mg BID in some patients based on clinical response.

Tofacitinib is an orally administered Janus kinase (JAK) inhibitor. In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimers containing JAK3 and/or JAK1 with functional selectivity over JAK2 homodimer signaling.

Inhibition of JAK1 and JAK3 by tofacitinib supposedly blocks signaling through the common gamma chain containing receptors for several cytokines, including IL-2, -4,-7,-9, -15 and -21. These cytokines are integral to lymphocyte activation, proliferation, and function and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will also likely results in attenuation of signaling by additional proinflammatory cytokines, such as IL-6 and interferon (IFN) γ. At higher exposures, inhibition of erythropoietin signaling could also occur via inhibition of JAK2 homodimer signaling.

Summary of information submitted

NDA 203214 consists of 13 in vitro studies with human materials, 21 Phase 1 studies, 8 Phase 2 studies (6 completed, 2 ongoing), 6 Phase 3 studies (4 completed, 2 ongoing, data from 5 trials are used to support efficacy and safety), and 12 population based modeling analyses. The clinical pharmacology information for Tofacitinib is mainly derived from Phase 1 studies as well as in vitro studies evaluating permeability, plasma protein binding, role of transporters, and potential for CYP 450 metabolic enzymes inhibition and induction. Population based modeling analyses including population pharmacokinetics analysis were performed to assess the effect of covariates and to understand the time course of effect and toxicities and their association with dose or exposure. In addition, 24 bioanalytical reports have been submitted to measure the levels of parent compound, main metabolites, co-administered drugs such as methotrexate, and PD markers such as CRP.

Rational for 5 mg bid and 10 mg dose selection

These doses were selected based on results of 2 dose ranging Phase 2 studies in patients with active rheumatoid arthritis of 6 months duration (Study ID: A3921035 and A3921025). Trial A3921035 tested tofacitinib as monotherapy in patients who have failed at least one DMARDs, while trial A3921025 tested tofacitinib in combination with methotrexate in patients who had inadequate response to methotrexate alone. These studies compared the effect of Tofacitinib on efficacy biomarkers such as ACR20, ACR50, ACR50, DAS28-3 (CRP) and safety endpoints such as change in hemoglobin, neutrophils, and LDLc across doses ranging from 1 mg bid to 15 mg bid and 20 mg qd.

Trial A3921035 demonstrated increase in ACR20 response (primary endpoint) with increase in dose from 1 to 15 mg bid, which plateaus at 10 mg bid, while in A3921025, except for 1 mg bid dose, the response was same for doses across 3 to 15 mg bid and 20 mg qd. In both trials, % incidences of mild or moderate anemia were higher than placebo for doses 10 mg bid and above. In trial A3921035, creatinine clearance declined by about 3 to 5 mL/min for doses 5 mg and above, while in trial A3921025 there was no clear dose dependent trend; however decline ranged from 2.5 to 9 mL/min for all tested dose levels including placebo.

Sponsor used the data from the trial A3921025 to do model based analysis for efficacy and safety endpoints. Efficacy endpoints were placebo adjusted response rates of at least 20%, 20%, and 15% respectively for ACR20, ACR50, and ACR70 at week 12. Safety endpoint was no more than 5% placebo adjusted incidence through 24 weeks of: (a) >2 g/dL decrease in hemoglobin from baseline or (b) an absolute hemoglobin level of <8 g/dL. *The doses with approximately 50% probability of achieving the target effect were considered for further evaluation*. Both 5 mg BID and 10 mg BID doses met these criteria (**Figure 1 A**) and were tested in Phase 3 trials.

Data from trial A3921019 showed that after 6 weeks of treatment, efficacy endpoints did not return to baseline in 2 weeks follow up (**Figure 1 B**), suggesting that pharmacodynamic activity is longer than pharmacokinetic half-life.

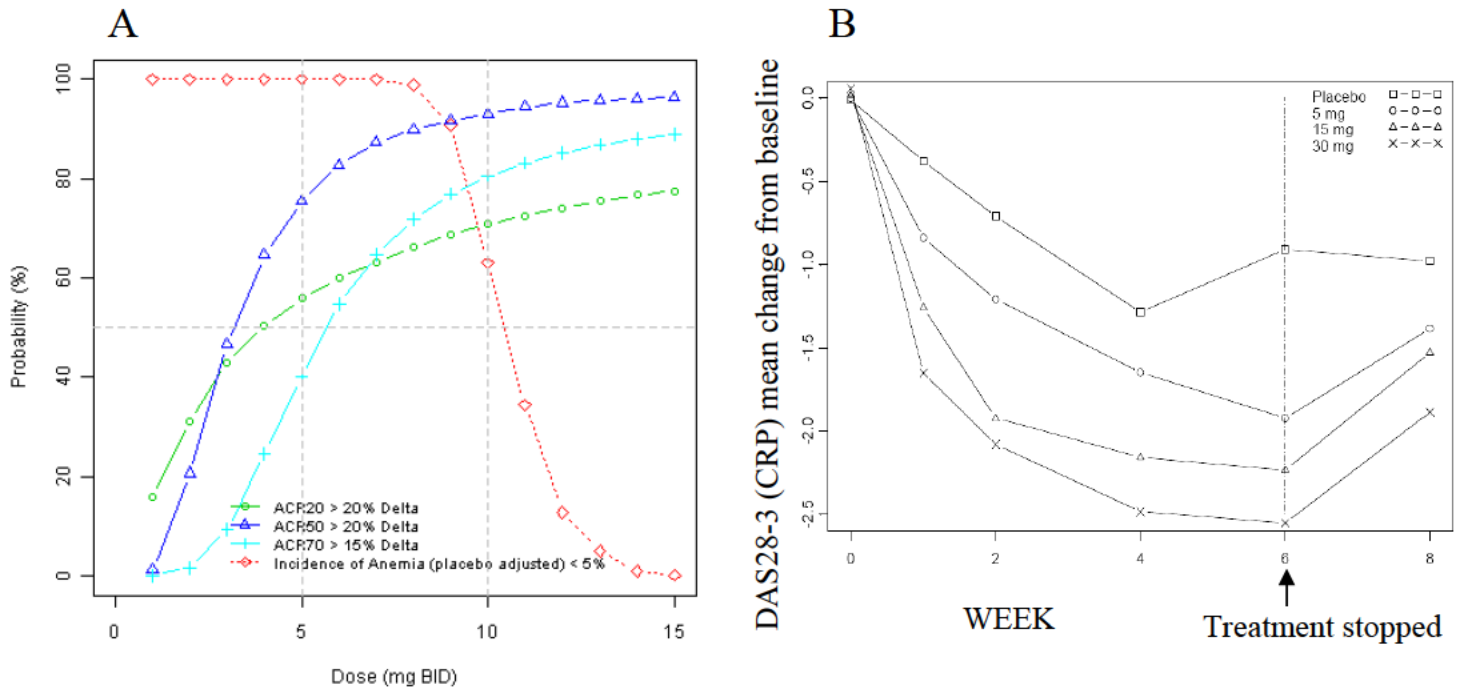


Figure 1. (A) Probability of achieving target effects for efficacy (ACR20, ACR50 and ACR70 response rates) and safety (anemia) endpoints based on dose response modeling of A3921025 data, and (B) DAS28-3 (CRP) mean change from baseline after 6 weeks of treatment for data from A3921019 clinical study

Efficacy in Phase 3 trials

The Phase 3 studies supporting the efficacy of Tofacitinib in rheumatoid arthritis patients included:

- Double-blind, placebo controlled, studies with a duration of treatment of 6 months to 24 months with tofacitinib given in background of methotrexate or DMARD therapies in patients with active rheumatoid arthritis (studies A3921032, A3921044, A3921046, and A3921064)
- A double-blind, placebo controlled trial of 6 months duration testing tofacitinib as monotherapy in patients with rheumatoid arthritis (study A3921045)

These Phase 3 studies compared the efficacy of Tofacitinib arm (5 mg bid or 10 mg bid) against placebo arm, when given alone or in combination with methotrexate or DMARD therapies. The placebo adjusted response rates for ACR20 endpoint from these trials are summarized in **Figure 2**.

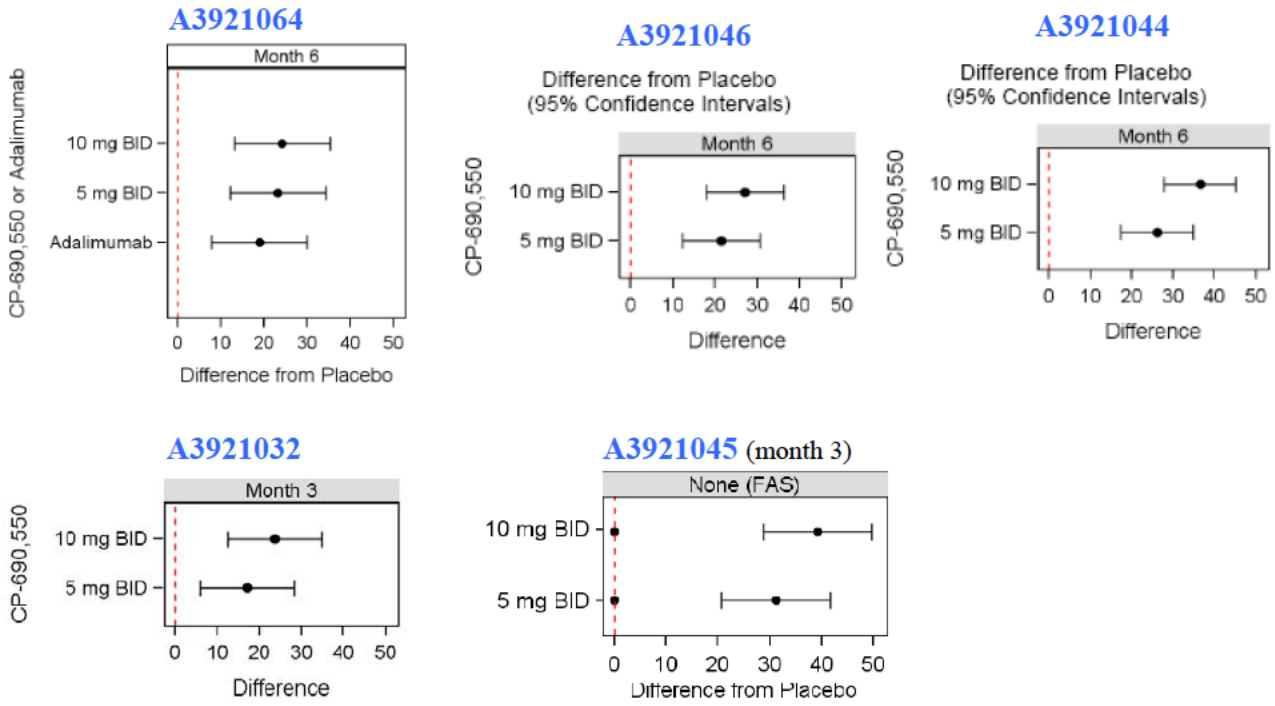


Figure 2. Placebo adjusted response rate and 90% confidence intervals for ACR20 endpoint from 5 Phase 3 trials

Effect of intrinsic/extrinsic factors on dose

As per sponsor's proposal, tofacitinib can be administered with or without food. No dose adjustments have been proposed based on studied intrinsic and extrinsic factors such as weight, age, gender, race, and co-administration with methotrexate. For hepatic impairment, no dose adjustment recommended for mild cases, maximum dose recommended for moderate cases is 5 mg bid, and impact of severe hepatic impairment has not been tested. For renal impairment, no dose adjustments are recommended for mild or moderate cases, and maximum dose recommended for severe cases is 5 mg bid. Co-administration with ketoconazole (CYP3A4 inhibitor) and fluconazole (CYP3A4 and CYP2C19 inhibitor) increases tofacitinib exposure by about less than and equal to 2 fold, and the maximum dose recommended is 5 mg bid. Following co-administration with rifampin, exposure decreases by about 2 fold, and sponsor proposes a caution statement 'may decrease efficacy'.

To-be-marketed formulation vs. clinical development formulation

The formulation used in all Phase 3 efficacy and safety clinical studies was different from the final to-be-marketed formulation and differs in following aspects:

1. Total tablet weight for 5 mg formulation used in Phase 3 trials was (b) (4) while for the to-be-marketed formulation it is 206 mg
2. Amount of inactive ingredients (b) (4) microcrystalline cellulose, (b) (4), lactose monohydrate, and croscarmellose sodium (b) (4)

Sponsor has demonstrated bioequivalence between Phase 2B, Phase 3, and to-be-marketed formulation in study A3921075.

Effect on QT interval

As per QT-IRT review, in a thorough QT study at a single supra-therapeutic dose (i.e., 100 mg) no clinically relevant QT prolongation was observed.

Pediatrics development plan

A waiver has been request for evaluation of safety and effectiveness of Tofacitinib in age group <2 years. For age group 2-18 years, sponsor has requested deferral to ensure that safety and efficacy is first established in adult patients.

Summary of Tofacitinib PK

The PK characteristics of Tofacitinib are summarized in **Figure 3**. Sponsor states that Tofacitinib has high aqueous solubility and moderate permeability, indicating to classification in BCS Class 3 category. After oral administration maximum concentrations (i.e., C_{max}) of Tofacitinib are reached in 0.5-1 hours. The absolute bioavailability of Tofacitinib after oral administration of 10 mg dose is approximately 74%. Data from preclinical studies indicate the involvement of P-gp transporter in intestinal absorption of Tofacitinib. Following co-administration with food rate of absorption was reduced (C_{max} was reduced by about 32%) but there was no effect on the extent of absorption (ie., AUC). Based on mass balance study, following oral administration, majority of drug was in form of parent compound in plasma (i.e., ~65%) and the rest in form of 8 different metabolites. Exposure of each metabolite was less than 8% of the total exposure, and their potency for JAK1/3 inhibition was less than or equal to 10% of the potency of parent.

Plasma protein binding for tofacitinib is moderate, primarily to albumin, with fraction unbound of 0.61. The volume of distribution at steady-state (V_{ss}) following a single 10 mg intravenous dose of tofacitinib to healthy subjects was approximately 87 liters, indicating extensive tissue distribution. The terminal half-life of tofacitinib is ~3 hours. After twice-daily dosing, steady-state plasma concentrations were reached by 24-48 hrs, with negligible accumulation.

Metabolism is reported to be the major pathway of clearance for tofacitinib, primarily through CYP3A4 with a minor contribution from CYP2C19. Approximately 80% of administered dose gets excreted in urine, 29% as unchanged drug and 51% as metabolites. The fecal elimination is minor with about 20% of administered dose (parent 7%, metabolite 13%) eliminated by this route.

Tofacitinib is not an inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. Tofacitinib was found to have a low potential to inhibit P-gp, OCT2-, OATP1B1, and OATP1B3 transporters *in vivo*. It's not a substrate of BCRP.

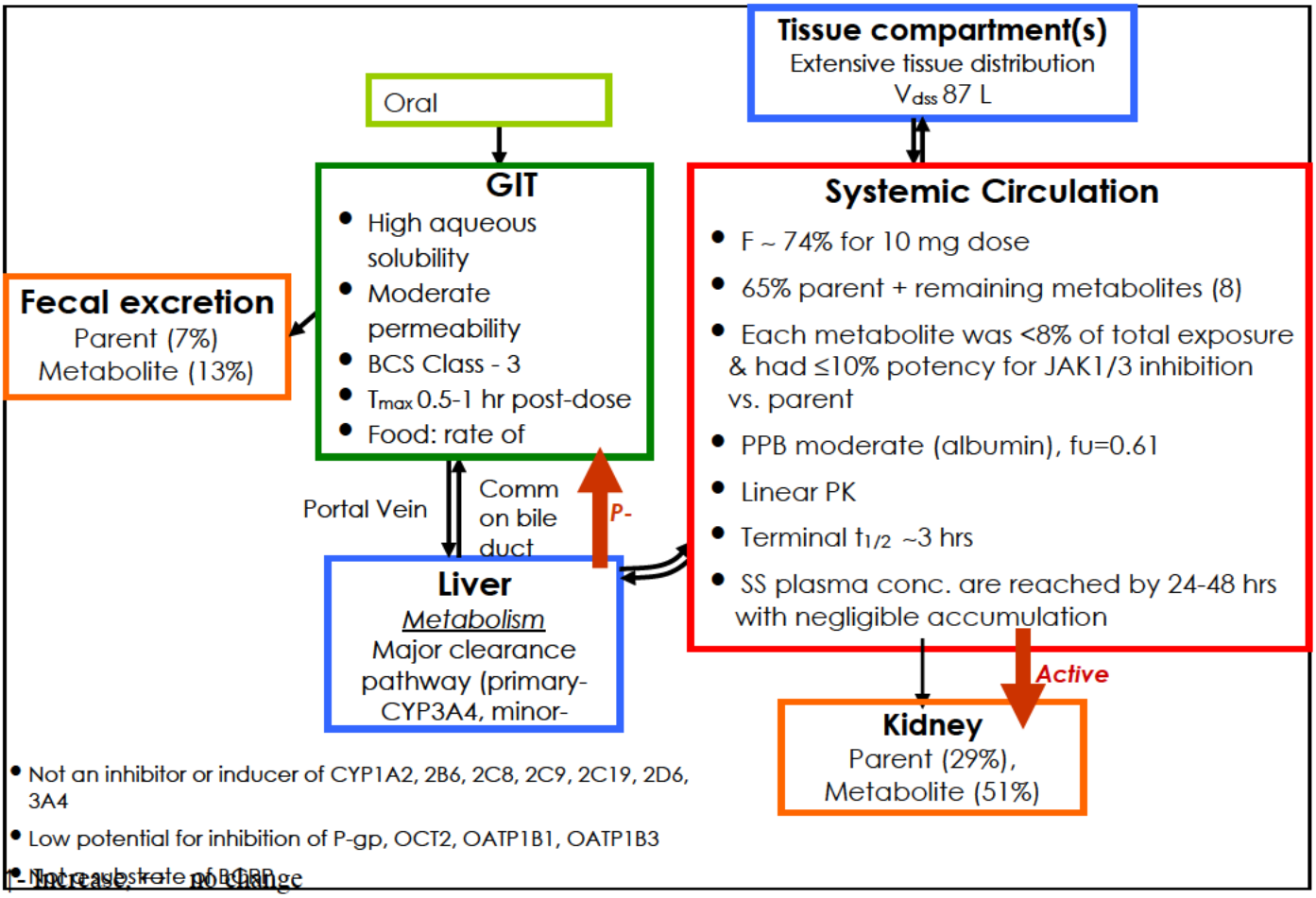


Figure 3: Schematic presentation of Tofacitinib PK properties

Summary of population based modeling analysis

Sponsor conducted population pharmacokinetic analysis, and several other population based modeling analysis for pharmacodynamic markers based on mechanism of action (such as C - reactive protein and lymphocyte counts) and for safety endpoints (such as hemoglobin, LDLc, neutrophils, ALT, serum creatinine, and blood pressure). Sponsor reported findings from these modeling based analyses are summarized in Table 1.

Table 1. Summary of Findings from Population Based Modeling Analyses

Endpoint	Dose range	Relationship
Mechanism of action based PD endpoints		
CRP	1-15 mg BID	• Dose-dependent reductions within 2 weeks with minimal additional decrease beyond 2 weeks • Median %reduction from baseline for 5 and 10 mg BID: 75-80%
Pan T-lymphocytes	1-30 mg BID	No consistent pattern
Helper T-lymphocytes with MHC-II	1-30 mg BID	No consistent pattern
Cytotoxic T-lymphocytes with MHC-I	1-30 mg BID	No consistent pattern
Natural Killer (NK) Cells	1-30 mg BID	• Dose-dependent decrease • nadir 8-10 wk • at nadir 36% & 47% reductions in NK cells from baseline for 5 and 10 mg dose • return to baseline within 4-wk of cessation of therapy • No clear association of lower NK cells with increased incidences of serious infection, herpes zoster, and malignancies
B-lymphocytes	1-30 mg BID	Dose-dependent increase
Safety endpoints		
Neutrophils	5-30 mg BID	• Dose-dependent reduction • stabilization of mean ANC by 6-8 weeks with no progressive decline thereafter, for treatment duration lasting over 2 years • 10 mg BID dose have 1.4 and 1.6 times increased risk of mild/moderate and severe neutropenia, relative to 5 mg BID

LDL	1-30 mg	• Dose-dependent increase, plateaus at 15 mg BID • patients with higher • baseline LDL-c levels showed smaller fractional increases relative to patients with lower baseline LDL-c concentrations • 13.4% and 18.1% increase from baseline for 5 and 10 mg BID dose
ALT	1-30 mg	• Dose dependent increase • background MTX had higher baseline and post-treatment ALT values than those without MTX usage • <1% of >3xULN increase at 5 and 10 mg doses
SCr	1-30 mg	• Similar increase for 5 & 10 mg dose • At wk 24: Non-Asian: 8.2-8.9%; Asian: 9.6-10.5% • From Phase 3 studies increase was 0.06 and 0.08 mg/dL for 5 and 10 mg BID, respectively, over 12 months • Study A3921033 in healthy subjects showed no effect on mGFR (iohexol serum clearance), CLCr, and renal plasma flow (PAH renal clearance) after 14 days of treatment • Study A3921152 planned for evaluation of effect of tofacitinib (42 days treatment) on mGFR in patients with active RA
BP	0.1-100 mg Phase 1; 1-30 mg Phase 2	• No dose-response • SBP increase of 0.3 and 0.6 mmHg for 5 and 10 mg BID over placebo, respectively • No differences in DBP
Serious infection & Malignancy	1-30 mg	• Serious infection: 1.3-1.9 times greater likelihood with 10 mg BID vs. 5 mg BID • Malignancy: no association with dose

Summary of drug-interaction studies

Effect of other drugs on Tofacitinib

Effect of co-administration of ketoconazole, fluconazole, rifampin, cyclosporine A, tacrolimus, and methotrexate on tofacitinib exposure (AUC) and C_{max} was evaluated. When given with ketoconazole (a potent CYP3A4 and P-gp inhibitor) tofacitinib AUC and C_{max} increased by 103% and 16%, respectively. With fluconazole (a CYP3A4 and CYP2C19 inhibitor) AUC and C_{max} increased by ~79% and ~30%, respectively. Sponsor recommended keeping the maximum dose to 5 mg bid in cases of co-administration with these drugs. For co-administration with rifampin (a potent CYP3A4 inducer), AUC and C_{max} decreased to 26% and 16% of that for the reference product, respectively. Co-administration with cyclosporine A, tacrolimus, and methotrexate did not have any significant effect on tofacitinib AUC and Cmax.

Effect of Tofacitinib on other drugs

Effect of tofacitinib co-administration on midazolam, methotrexate, and ethinylestradiol AUC and C_{max} was evaluated. No significant change in AUC and C_{max} was observed for any of the studied drug.

<u>Mid-Cycle Deliverables</u>

Following are the Mid-Cycle Deliverables;

- Any approvability issues
- Dose Selection
- Exposure-Response Evaluation for Efficacy and Safety
- Drug-drug Interaction and Extrinsic/Intrinsic Factors
- Labeling

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/s/

LOKESH JAIN
12/14/2011

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12/14/2011