

December 27, 2021

THE CONTROLLER OF PATENT
THE PATENT OFFICE
BOUDHIK SAMPAD A BHAWAN, PLOT NO. 32
SECTOR 14, DWARKA, NEW DELHI-110078

**Re: REPRESENTATION u/s 25(1) of the Patent act – By SANKALP
REHABILITATION TRUST against Indian Patent Application No.
8222/DELNP/2015 filed on 10/09/2015
Applicant: PFIZER INC.
R&A Ref. No.: OPP0397**

Respected Sir,

We submit herewith Pre-Grant Opposition under Section 25(1) of the Patent Act, 2005 and Form 7A.

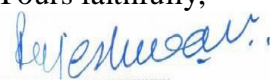
The Learned Controller is requested to take the documents on record and proceed further in the matter and keep the Petitioner advised of each and every step taken in the matter.

We crave the leave of the Learned Controller to submit additional documents or evidence or if necessary to support any of the averments in the representation as may be necessitated in the proceeding.

Lastly, we request the Learned Controller to grant an opportunity of being heard before the above representation is finally decided.

Thanking you,

Yours faithfully,



RAJESHWARI H. IN/PA – 0358
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

Encl: As stated

C.C: LAKSHMI KUMARAN & SRIDHARAN
B-6/10, Safdarjung Enclave,
New Delhi - 110 029, India
E-mail: iprdel@lakshmisri.com;

Also at: A - 202, First Floor, Shivalik Enclave, Malviya Nagar, New Delhi-110017

BEFORE THE CONTROLLER OF PATENTS, NEW DELHI

IN THE MATTER OF:

The Patents Act, 1970 as amended by the Patents (Amendment) Act 2005, and The Patents Rules, 2003, as amended by The Patents (Amendment) Rules, 2006

AND

IN THE MATTER of Pre-grant opposition under Section 25(1)

AND

IN THE MATTER of Indian Patent Application No. 8222/DELNP/2015

IN THE MATTER OF:

SANKALP REHABILITATION TRUST

..... OPPONENT

VS.

PFIZER INC.

.....APPLICANT

PRE-GRANT OPPOSITION BY SANKALP REHABILITATION TRUST

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Dated this day 27th of December, 2021



RAJESHWARI H. IN/PA – 0358
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI

FORM 7A
THE PATENTS ACT,
1970 (39 OF 1970)
AND
THE PATENTS RULES, 2003
REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT
[See Rule 55]

We, **SANKALP REHABILITATION TRUST**, having its registered office at SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002, India, hereby give Notice of opposition to the grant of patent in respect of Indian Patent Application No. 8222/DELNP/2015 filed on 10/09/2015 made by **PFIZER INC.** on the grounds.

- (a) Section 25(1)(b): Lack of novelty
- (b) Section 25(1)(e): Lack of inventive step
- (c) Section 25(1)(f): Invention is not patentable under section 3(d) and 3(e)
- (d) Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
- (e) Section 25(1)(h): Failed to disclose to the Controller the information required by section 8.

(Detailed grounds are set out in the Opposition)

Our address for service in India is:

RAJESHWARI & ASSOCIATES
A – 202, FIRST FLOOR
SHIVALIK ENCLAVE
MALVIYA NAGAR
NEW DELHI – 110017
INDIA
Tel: + 91-11-41038911
Fax: +91-11-43851067
Mobile No. 9910206718
Email: rajeshwari@ralegal.co.in; opposition@ralegal.co.in;

Dated this 27th day of December, 2021



RAJESHWARI H. IN/PA – 0358
 OF RAJESHWARI AND ASSOCIATES
 AGENT FOR THE OPPONENT

TO
 THE CONTROLLER OF PATENTS
 PATENT OFFICE, NEW DELHI

BEFORE THE CONTROLLER OF PATENTS, THE PATENT OFFICE**NEW DELHI**

In the matter of Section 25(1) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of Rule 55 of The Patents Rules 2003 as amended by the Patent (Amendment) Rules, 2006

And

IN THE MATTER of Indian Patent Application 8222/DELNP/2015 filed on 10/09/2015 in the name of **PFIZER INC.**

REPRESENTATION BY:**SANKALP REHABILITATION TRUST****..... OPPONENT****VS.****PFIZER INC.****.....APPLICANT****REPRESENTATION BY WAY OF PRE-GRANT OPPOSITION UNDER****SECTION 25(1) OF THE PATENTS ACT, 1970**

1. We, **SANKALP REHABILITATION TRUST**, is a community based non-profit organisation seeking to prevent and treat HIV/AIDS, and having its registered at SS Bengali Municipal School, First Floor, Thakurdwar Road, Charni Road East, Mumbai – 400002, India, hereby submit my representation by way of opposition to the grant of

patent in respect of Indian Patent Application 8222/DELNP/2015 dated 10/09/2015 in the name of PFIZER INC. entitled “TOFACITINIB ORAL SUSTAINED RELEASE DOSAGE FORMS”.

STATEMENT OF CASE OF OPPONENT

2. The Opponent has learnt that the Applicant has filed an Indian Patent Application No. 8222/DELNP/2015 (hereinafter “the Impugned Patent Application”) on 10/09/2015. The impugned patent application was published in the official journal of the patent office on 31/08/2016, which is currently pending before the Patent Office. The Impugned Patent Application has a priority date 16/03/2013.
3. The Impugned Patent Application is entitled “TOFACITINIB ORAL SUSTAINED RELEASE DOSAGE FORMS”.
4. The Opponent by way of this present pre-grant opposition submits that the claims currently pending on record are not patentable under the provisions provided in this Act. The claims currently on record are annexed herewith as **Annexure-1** and reproduced herein below for ready reference:

I/We Claim:

1. A once daily pharmaceutical dosage form comprising a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen, and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer, wherein said dosage form is a sustained release dosage form, and when added to a test medium comprising 900 ml of 0.05M pH 6.8 potassium phosphate buffer at 37° C in a standard USP rotating paddle apparatus and the paddles are rotated at 50 rpm, dissolves not more than 30% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 1 hour, and not less than 35% and not more than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 2.5 hours and not less than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 5 hours and wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to a subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib, or pharmaceutically acceptable salt thereof.

2. A once daily pharmaceutical dosage form comprising a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen, and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer, wherein the dosage form is a sustained release dosage form and when administered orally to a subject provides an AUC in the range of 80% to 125% of the AUC of 5 mg of tofacitinib or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof administered as an immediate release formulation BID and provides a ratio of geometric mean plasma C_{max} to C_{min} from about 10 to about 100 and wherein the dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to the subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib or pharmaceutically acceptable salt thereof.

3. The pharmaceutical dosage form of claim 2, wherein the AUC range is 90% to 110% and the geometric mean plasma concentration C_{max} to C_{min} from about 20 to about 40.

4. The pharmaceutical dosage form of claim 3, wherein the geometric mean plasma concentration C_{max} to C_{min} from about 20 to about 30.

5. The pharmaceutical dosage form of claim 2, wherein when the dosage form is administered orally to the subject provides a mean plasma C_{max} in the range of 70% to 125% of the mean plasma C_{max} of tofacitinib administered as the immediate release formulation BID at steady state.

6. The pharmaceutical dosage form of claim 2, wherein when the dosage form is administered orally to the subject provides a drug holiday in the range of 80% to 110% of the drug holiday of tofacitinib administered as the immediate release formulation BID over a 24 hour period.

7. The pharmaceutical dosage form of claim 2, having a drug holiday from about 15 to about 18 hours over the 24 hour period.

8. A once daily pharmaceutical dosage form comprising

a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen,

and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer,

wherein said dosage form is a sustained release dosage form, and when administered to a subject has a mean area under the plasma concentration versus time curve following administration from about 17 ng-hr/mL per mg of tofacitinib dosed to about 42 ng-hr/mL per mg of tofacitinib dosed and a ratio of geometric mean plasma C_{max} to C_{min} from about 10 to about 100 and wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to the subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib or pharmaceutically acceptable salt thereof.

9. The pharmaceutical dosage form of claim 8, wherein the ratio of geometric mean plasma C_{max} to C_{min} from about 20 to about 40.

10. The pharmaceutical dosage form of claim 9, wherein the ratio of geometric mean plasma C_{max} to C_{min} from about 20 to about 30.

11. The pharmaceutical dosage form of claim 8, wherein the subject has a single, continuous time above about 17 ng/ml from about 6 to about 15 hours and a single, continuous time below about 17 ng/ml from about 9 to about 18 hours over a dosing 24 hours interval.

12. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time above about 17 ng/ml from about 6 to about 9 hours.
13. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time below about 17 ng/ml from about 15 to about 18 hours.
14. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time above about 17 ng/ml from about 11 to about 15 hours.
15. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time below about 17 ng/ml from about 9 to about 13 hours.
16. The pharmaceutical dosage form of claim 8, wherein the subject has a mean maximum plasma concentration (C_{max}) from about 3 ng/mL per mg to about 6 ng/mL per mg of tofacitinib dosed.
17. The pharmaceutical dosage form of claim 8, wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, by a system selected from the group consisting of an extrudable core system, a swellable core system, and an asymmetric membrane technology.
18. The pharmaceutical dosage form of claim 8 wherein, said cellulose derivative is cellulose acetate.
19. The pharmaceutical dosage form of claim 8, wherein said coating further comprising a water soluble polymer having an average molecular weight between 2000 and 100,000 daltons.
20. The pharmaceutical dosage form of claim 19, wherein said water soluble polymer is selected from the group consisting of water soluble cellulose derivatives, acacia, dextrin, guar gum, maltodextrin, sodium alginate, starch, polyacrylates, and polyvinyl alcohols.
21. The pharmaceutical dosage form of claim 20, wherein said water soluble cellulose derivatives comprises hydroxypropylcellulose, hydroxypropylmethylcellulose or hydroxyethylcellulose.
22. The pharmaceutical dosage forms of claim 8, wherein the osmagen is a sugar.
23. The pharmaceutical dosage form of claim 22, wherein the sugar is sorbitol.
24. The once daily pharmaceutical dosage form of claim 8 wherein the subject has a mean steady-state minimum plasma concentration (C_{min}) less than about 0.3 ng/mL per mg of tofacitinib dosed.
25. The once daily pharmaceutical dosage form of claim 8, wherein when administered orally to the subject has a mean fed/fasted ratio of the area under the plasma concentration versus time curve from about 0.7 to about 1.4 and a mean fed/fasted ratio of the maximum plasma concentration (C_{max}) from about 0.7 to about 1.4.

5. **Impugned Patent Application:** The present pre-grant opposition is against Indian Patent Application 8222/DELNP/2015 dated 10/09/2015 in the name of PFIZER INC. titled “TOFACITINIB ORAL SUSTAINED RELEASE DOSAGE FORMS” and is drawn towards the oral sustained release compositions of 3-((3R, 4R)-4-methyl - 3 - [methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino] - piperidin - 1-yl)-3-oxopropionitrile (hereinafter Tofacitinib), which is useful as an inhibitor of protein kinases, such as the enzyme Janus Kinase (JAK).
6. The impugned invention provides sustained release formulations comprising Tofacitinib or pharmaceutically acceptable salts thereof and formulations have desirable pharmacokinetic characteristics. Examples include AUC, C_{max} , dose-adjusted AUC, dose-adjusted C_{max} , and fed/fasted AUC and C_{max} ratios.
7. The presently claimed dosage forms are osmotic sustained release formulations suitable for once daily administration in the form of a core comprising Tofacitinib and a semi-permeable membrane coating comprising a cellulose derivative which have the specific in vitro release profile specified in claim 1.
8. **PRIOR ARTS:** The opponent wishes to rely on the following prior arts as evidence in support of the grounds of opposition.
 - i. WO 2012/100949 published on 02 August 2012 (**annexed herewith as Annexure – 2**);
 - ii. Clinical Pharmacology and Biopharmaceutics Review, Center For Drug Evaluation And Research, 2011;
 - iii. D. Prabakaran, Effect of hydrophilic polymers on the release of diltiazem hydrochloride from elementary osmotic pumps, International Journal of Pharmaceutics 259 (2003) 173–179;

- iv. Ying-Ku Lin, Investigations on the drug releasing mechanism from an asymmetric membrane-coated capsule with an in situ formed delivery orifice, Journal of Controlled Release 89 (2003) 57–69;
9. It is submitted that all claims of the impugned patent application are liable to be refused on following grounds as below, which are without prejudice to each other:
- (a) Section 25(1)(b): Lack of novelty
 - (b) Section 25(1)(e): Lack of inventive step
 - (c) Section 25(1)(f): Invention is not patentable under section 3(d) and 3(e)
 - (d) Section 25(1)(g): The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.
 - (e) Section 25(1)(h): Failed to disclose to the Controller the information required by section 8.

GROUND 1: Section 25(1)(b) Lack of Novelty

10. It is submitted that claims 1 to 25 are not novel, and therefore have to be rejected under Section 25(1)(b) of the Act.
11. The impugned patent application lacks novelty in view of WO 2012/100949 (WO'949). This document was published on 02 August 2012 which is prior to priority date of impugned patent application i.e. 16/03/2013.
12. WO'949 discloses oral modified release dosage forms of Tofacitinib which may be in the form of a matrix dosage form, in the form of a core & shell or in the form of a multiple unit pellet system.

13. The oral modified release solid dosage forms of WO'949 are for once daily administration comprising Tofacitinib, in particular 4.0 to 12 mg, and a non-erodible material.
14. Osmotic controlled release devices are contemplated and illustrated by WO'949 in Example 10. Example 10 of WO'949 specifically discloses an osmotic tablet comprising a core comprising Tofacitinib and a coating comprising polyethylene glycol 3350 and cellulose acetate.
15. One embodiment of WO'949 refers to osmotic controlled release tablets comprising:
 - (A) a core comprising Tofacitinib and an osmotic agent (which may be an aqueous-swellable hydrophilic polymer or an osmogen), and
 - (B) a water-permeable coating comprising a non-erodible polymer.
16. Also described in WO'949 are osmotic controlled release tablets comprising a core comprising Tofacitinib and an osmotic agent and a water-permeable coating comprising a non-erodible polymer. Suitable non-erodible polymers are described therein and include as preferred embodiments cellulose ethers, cellulose esters, Copolymers of methacrylic acid or methacrylic acid esters and Polyvinyl acetate or polyvinyl acetate copolymers.
17. WO'949 also discloses that the dosage form may comprise a core comprising the Tofacitinib and a coating wherein the core comprises a swellable polymer, the dosage form delivers Tofacitinib by osmotic pressure, and the coating may comprise cellulose acetate (a "water insoluble polymer" and a "cellulose derivative" which provides a semi-permeable membrane).

18. WO'949 further discloses that the dosage form may comprise a water soluble polymer such as hydroxypropylmethyl cellulose, hydroxypropylcellulose, or polyvinyl alcohol.
19. WO'949 discloses that the core of the dosage form may comprise a sugar or sugar alcohol such as sorbitol and the coating on the osmotic core may further comprise polyethylene glycol, a "water soluble polymer" having a molecular weight of 3350.
20. With these dosage forms of WO'949, the drug is gradually released in a specific in vitro dissolution profile.
21. The presently claimed dosage forms are osmotic sustained release formulations suitable for once daily administration in the form of a core comprising Tofacitinib which is surrounded by a semi-permeable membrane coating comprising a cellulose derivative, said dosage forms are characterized by: a particular in vitro release profile in claim 1, particular pharmacokinetic parameters AUC & C_{\max} to C_{\min} .
22. As elaborated in preceding paragraphs all the technical features of the composition claimed in the impugned application are disclosed in the prior art document WO'949.
23. Defining a composition and establishing the novelty in functional terms does not suffice in the absence of a novelty of structural features or elements of the claimed composition.
24. It is well settled legal tenant that assessment of patentability of an invention cannot be based on merely on what the composition does rather than what it is i.e. in absence of novel and inventive technical features of a claimed composition, merely functional features cannot be the sole basis for assessment of patentability.

25. Hence, every feature of claimed composition is already disclosed in the prior art. Therefore, the impugned application lacks novelty over WO'949 and the impugned application ought to be rejected on this ground alone.

GROUND 3: Section 25(1)(e) Lack of Inventive Step

26. It is submitted that the invention as claimed is obvious and does not involve any inventive step in view of whatever was known and published in India or elsewhere prior to the priority date of impugned patent application i.e. prior to 06/03/2015 the earliest claimed priority.
27. It is submitted that all the claims of the impugned application are not inventive and are obvious in view of common general knowledge in art and combined with teachings of above-mentioned prior arts.
28. WO'949 discloses oral modified release dosage forms of Tofacitinib which may be in the form of a matrix dosage form, in the form of a core & shell or in the form of a multiple unit pellet system.
29. The oral modified release solid dosage forms of WO'949 are for once daily administration comprising Tofacitinib, in particular 4.0 to 12 mg, and a non-erodible material.
30. Osmotic controlled release devices are contemplated and illustrated by WO'949 in Example 10. Example 10 of WO'949 specifically discloses an osmotic tablet comprising a core comprising Tofacitinib and a coating comprising polyethylene glycol 3350 and cellulose acetate.

31. One embodiment of WO'949 refers to osmotic controlled release tablets comprising:
- (A) a core comprising Tofacitinib and an osmotic agent (which may be an aqueous-swellable hydrophilic polymer or an osmogen), and
 - (B) a water-permeable coating comprising a non-erodible polymer.
32. Also described in WO'949 are osmotic controlled release tablets comprising a core comprising Tofacitinib and an osmotic agent and a water-permeable coating comprising a non-erodible polymer. Suitable non-erodible polymers are described therein and include as preferred embodiments cellulose ethers, cellulose esters, Copolymers of methacrylic acid or methacrylic acid esters and Polyvinyl acetate or polyvinyl acetate copolymers.
33. WO'949 discloses that the dosage form may comprise a core comprising the Tofacitinib and a coating wherein the core comprises a swellable polymer, the dosage form delivers Tofacitinib by osmotic pressure, and the coating may comprise cellulose acetate (a "water insoluble polymer" and a "cellulose derivative" which provides a semi- permeable membrane).
34. WO'949 further discloses that the dosage form may comprise a water soluble polymer such as hydroxypropylmethyl cellulose, hydroxypropylcellulose, or polyvinyl alcohol.
35. WO'949 discloses that the core of the dosage form may comprise a sugar or sugar alcohol such as sorbitol and the coating on the osmotic core may further comprise polyethylene glycol, a "water soluble polymer" having a molecular weight of 3350.
36. With these dosage forms of WO'949, the drug is gradually released in a specific in vitro dissolution profile in a prolonged manner.

37. It is submitted that the drug Tofacitinib was approved for medicinal use by various regulatory authorities including US Food and Drug Administration before the priority date of the present application (*Re Clinical Pharmacology and Biopharmaceutics Review, Center For Drug Evaluation And Research, 2011, annexed herewith as Annexure 3*). From the *Clinical Pharmacology and Biopharmaceutics Review* published report it was known to a person skilled in the art that Tofacitinib, a weakly basic compound, is classified as a BCS Class 3 compound (high solubility, moderate permeability) and has demonstrated dose proportionality for AUC_{inf} over a range of 1–100 mg.
38. Further, Hutmacher et al in their 2008 publication, (**as annexed herewith Annexure – 4**), studied the pharmacokinetics of QD and BID dosage regimen of Tofacitinib (Tofacitinib has been referred to by its code name CP-690,550 in said document).
39. Hutmacher et al discloses about Tofacitinib that “*the PK half-life was short relative to the dosing interval, the trough effect site concentration, C_e , was nearly a scalar multiple of the effective dose, D_e ...Because of the half-life is relatively short, the difference between C_e and D_e is within a decimal point at each trough*”.
40. Hutmacher et al disclosed in their 2008 publication, the methodology to characterize the exposure-response relationship between Tofacitinib and a discrete clinical endpoint for an informed selection of doses and dosage regimen design.
41. Hutmacher et al also disclose indirect response models which provide a semi-mechanistic framework for linking pharmacodynamic (PD) responses to plasma concentrations (PK) and for deriving dose–response (D-R) model parameters which would be consistent with respect to the concentration-response C-R model parameters.

Hutmacher disclose clear arithmetic modelling equations which correlate plasma drug concentration, AUC, and other pharmacokinetic parameters with the dose of the drug.

42. Thus, a person skilled in the art can arrive at the required dose and/or concentration of the drug released based on the desired response or based on the desired pharmacokinetic parameter such as plasma drug concentration and/or AUC.
43. It is generally known in the field that osmotic devices are most promising strategy based systems for controlled drug delivery. They are among the most reliable controlled drug delivery systems and could be employed as oral drug delivery systems or implantable devices.
44. It is commonly known in literature by way of several publications such as Theeuwes 1975 Prabakaran 2003 Gupta 2009, Ying-Ku Lin 2003 [**annexed herewith as Annexure 5, 6, and 7**] that osmotic drug delivery systems are unique in the sense that the delivery of drug(s) is not dependent/influenced by physiological variables within the GIT, these systems are adaptable to a number of drugs with minor modifications and the delivery of drug(s) can be predictably controlled in a useful manner.
45. Further, the factors which affect drug release from osmotic systems, the release mechanism of drug with various solubility modulators, the materials of construction and structural configurations of osmotic delivery systems are well known in the art.
46. Hence, formulation of a modified release formulation to achieve once daily administration (QD) of Tofacitinib was taught by WO'949. Besides this from the USFDA approval document and Hutmacher publication it was known that Tofacitinib displays dose proportionality for plasma concentration, AUC and response.

47. Thus, a person skilled in the art understands that since the drug release from the modified-release formulation of WO'949 is very slow the plasma drug concentration at a given period of time would also be accordingly less and in order to increase plasma drug concentration is to increase the dose of the drug or to increase the amount of drug released at the absorption site.
48. Hence, a person skilled in the art understands that in order to increase the plasma drug concentration from the once daily (QD) formulation, the rate of drug release from the modified formulation should be increased to an extent that larger amount of drug is release at the site of absorption.
49. Further, as per the common general knowledge in the field at the time of invention a person skilled in the art understood that osmotic delivery system is the best forms of controlled drug delivery system to achieve delivery of drug in highly predictable manner and the use of same to deliver once daily dosing of Tofacitinib was already taught by prior art WO'949. WO'949 also teaches the water soluble polymers, water insoluble polymers and osmogens which are suitable to be used with Tofacinib.
50. In light of the above knowledge available in the field at the time of the invention and clearly defined pharmacokinetic and pharmacodynamic parameters of the drug including dose proportionality (Re USFDA Clinical and Bio pharmaceuticals Review and Hutmacher et al), it was matter of arithmetic calculation for a person skilled in the art to arrive at the percentage drug to be released in order to achieve same plasma drug concentration and AUC as that achieved by IR formulation. Furthermore, it was merely a matter of routine experimentation to optimize the quantity of osmogen and in the osmotic delivery system so releases drug at a rate so that plasma drug concentration and AUC achieved is equivalent to that achieved by IR formulation.

51. Therefore, the claimed invention of the impugned application is merely a result of routine optimization rather than application of inventive faculty and human ingenuity. Thus, the claimed subject matter is obvious and devoid of any inventive merit.
52. The Applicant has asserted that presently claimed composition provides same it was surprisingly found that the bioavailability of Tofacitinib is reduced as the duration of release is prolonged, thereby requiring increased amounts of Tofacitinib to be administered in the sustained release dosage form to provide efficacious blood levels to subjects. However, increased amounts of Tofacitinib may cause over inhibition of JAK3 and/or JAK1 signalling and could compromise the body's immune system (refer page 4 of the "as filed" specification of the instant Application). Thus, at the time of the present invention, a person skilled in the art would have sought to avoid elevated levels of the maximum blood plasma concentration of Tofacitinib.
53. However, from the disclosure of USFDA Clinical and Biopharmaceutics Review and Hutmacher et al it was known that Tofacitinib exhibits dose proportionality for AUC_{inf} over a range of 1–100 mg. Therefore, it was known to a person skilled in the art that that the bioavailability of Tofacitinib is reduced as the duration of release is prolonged i.e. the plasma drug concentration decreases as the amount of drug (dose) available at the site of absorption is reduced.
54. Moreover, it is a known understanding in the field of immunosuppressants that excessive amounts of drug and/or prolonged periods of exposure to high dose of immunosuppressant drug unduly compromises body's immune system.

55. Keeping in view the above, a sustained release formulation which releases the drug in sufficiently high rate so as to match the plasma drug profile achieved by IR formulation is the expected route to be followed by a formulator.
56. Therefore, the Applicant has failed to establish any unexpected effect of the claimed composition which may be considered as significant contribution to the field of endeavour. Thus, the claimed dosage form lacks technical advancement.
57. In view of the above submissions, impugned application lacks inventive step and therefore, should be rejected on this ground alone.

GROUND 3: Claims not patentable under Section 25(1)(f)

The claimed subject matter is not patentable under Section 3(d) of the Act

58. It is submitted that the impugned patent application should not be allowed under Section 3(d) which states that “*the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*”

Explanation -For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy.”

59. The Opponent submits that the Applicant has failed to demonstrate any enhancement in the therapeutic efficacy with respect to composition which was already known at the time of the invention.
60. It is submitted that Tofacitinib IR formulation was already approved before the priority date of impugned application.
61. The Applicant has asserted in the specification as filed that the claimed dosage form of present invention provides once daily dosing as compared to the twice daily dosing which was conventionally being followed in case of IR 5mg tablets which may translate to increased patient compliance.
62. However, the Opponent submits that the claimed dosage form does not result in enhancement in therapeutic efficacy.
63. In a post priority publication of a randomized clinical trial conducted by the Applicant [*Re S. Mitrovic, Safety of Glucocorticoids For Early Rheumatoid Arthritis: A Meta-Analysis of Randomised Controlled Trials, annexed herewith as Annexure 8*], it was observed that the AUC_{inf} and C_{max} obtained by MR (modified release formulation) and AUC_{inf} and C_{max} obtained by IR (immediate release formulation) of Tofacitinib are equivalent.
64. In another post priority publication by the Applicant's clinical pharmacology team [*Manisha Lamba et al, Extended-Release Once-Daily Formulation of Tofacitinib: Evaluation of Pharmacokinetics Compared With Immediate-Release Tofacitinib and Impact of Food, The Journal of Clinical Pharmacology 2016, 56(11) 1362–1371, annexed herewith as Annexure 9*] it is stated that extended release once daily “*tablet formulation of Tofacitinib has been designed to achieve equivalence in total systemic*

exposure, as measured by area under the plasma concentration-time curve (AUC), relative to the IR formulation administered BID. In addition, the XR formulation was engineered to provide similarity in other PK parameters, including maximum (C_{max}) and minimum plasma concentration (C_{min}) compared with the IR formulation.”

65. It is further stated in said publication that *“The 10% increase in total daily dose of the XR formulation was necessary to match the AUC with the IR formulation.”*

66. Thus, rather than providing any enhancement in therapeutic efficacy, the claimed dosage form of impugned application requires higher amount of drug to be administered to a patient as compared to known conventional dosage form of Tofacitinib.

67. Therefore, the claimed subject matter of the impugned application has no enhancement of therapeutic efficacy and the impugned application should be rejected on this ground alone.

Claims of impugned application is not patentable as per Section 3(e) of the Act

68. Section 3(e) which clearly states that a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance is not patentable.

69. The Opponent states that the subject matter of impugned application is drawn to dosage form which is an admixture of various components which result in release of drug at certain rate.

70. As elaborated in preceding paragraphs under the heading of Inventive Step, it is common knowledge in art that Tofacitinib has very short T_{half} and its plasma drug concentration and AUC are proportional to the dose of the drug and therefore, osmotic delivery systems which are characterized by high predictability of drug release rate and that the drug release from said system can be modulated based on well established models and equations.

71. Thus, the Applicant has failed to demonstrate any unexpected effect of the claimed composition in the impugned specification.

72. In absence of any unexpected effect of the claimed composition established in the impugned specification, the claimed composition of the impugned application, the claimed subject matter of the impugned application is merely an admixture which falls under the prohibition of Section 3(e) read with Section 25(1)(f) of the Act. Thus, impugned application is liable to be rejected on this ground alone.

GROUND 5: INSUFFICIENCY OF DISCLOSURE

73. The complete specification does not sufficiently and clearly describe the invention or the method by which it is to be performed.

74. The Opponent states that it is a well settled rule that the specification should clearly and fairly describe the invention and disclose the best mode of working the invention so that the person skilled in the art could perform the invention without any undue efforts and it is hereby stated that the Applicant has failed to do so.

75. It is submitted that claims are not fairly based on the specification and complete specification does not describe the invention and the method of performing the invention.
76. The exemplified and tested compositions represent only a fraction of the species of compositions that lie within the scope of the claims, provided they achieve the recited functional limitations. Consequently, the specification, by failing to disclose any correlation between structure and function, does not provide guidance as to which of these ingredients in which amounts in which configurations would result in compositions within the scope of the claims. Therefore, the specification does not provide an adequate description of the claimed genus.
77. The Applicant has described one type of bilayer osmotic capsule having specific ingredients and amounts of said ingredients and having a specific structural arrangement, one type of hydrophilic matrix controlled release tablet having specific ingredients and amounts of said ingredients and specific hardness properties, one type of extrudable core system osmotic tablet having specific ingredients and amounts of said ingredients and specific thickness and hardness, and one type of extrudable tablet having specific ingredients and amounts of said ingredients and specific thickness and hardness.
78. The instant disclosure tests compositions having specific structures and properties and made by specific methods as follows:
- Examples 10-11 of the instant specification discloses a bilayer osmotic capsule comprising a tablet comprising specified amounts of polyethylene oxide, magnesium stearate, and Tofacitinib citrate compressed to a target

thickness of 15.6 mm. The capsule further comprises a sweller layer comprising specified amounts of polyethylene oxide coagulant grade, sodium chloride, microcrystalline cellulose, FC% C blue No2 lake dye, and magnesium stearate. The capsule further comprises a shell comprising specified amounts of polysorbate 80, cellulose acetate, and polyethylene glycol 3350. A single hole was drilled into the capsule body.

- Examples 4 and 12 disclose a hydrophilic matrix controlled release tablet comprising specified amounts of Tofacitinib, methocel K1 00LV, lactose monohydrate, and magnesium stearate which is compressed to a target hardness of 15 kP.
- Example 1 discloses an extrudable core system osmotic tablet comprising specified amounts of Tofacitinib citrate, sorbitol, hydroxyethylcellulose, copovidone, and magnesium stearate, which is compressed to an average thickness of 5.35 mm and a target hardness of 15 kP. The tablets were coated with a coating solution comprising specified amounts of hydroxypropyl cellulose and cellulose acetate to obtain a coating of 6%.
- Example 18 discloses an extrudable tablet comprising specified amounts of Tofacitinib citrate, sorbitol, hydroxyethylecellulose, copovidone, and magnesium stearate that is compressed to an average thickness of 4.17 mm and a target hardness of 11 kp.
- The tablet was coated with cellulose acetate and hydroxypropyl cellulose until a wet weight gain of 7% was achieved. A single hole was drilled in the tablet. Examples 15-18 tested certain compositions and found that

some can exhibit pharmacokinetic properties within functional parameters that are recited by the instant claims.

79. However, none of the claims of the impugned application are limited to dosage forms having all of the specific ingredients, amounts of ingredients, or structural configuration of said ingredients that are taught by the foregoing Working Examples.

80. Presently pending claims encompass the use of ANY ingredients in ANY amounts in the core, ANY osmogen in ANY amounts, and ANY water insoluble polymer and ANY other ingredients in ANY amounts in the semi-permeable membrane coating.

81. The specification does not appear to disclose any known general correlation between the structure of controlled release Tofacitinib compositions and the ability to obtain a composition that achieves the claimed pharmacokinetic parameters (other than that the specific compositions that are exemplified and tested in the disclosure can achieve these properties), that is sufficient to allow one of ordinary skill to determine which compositions comprising which ingredients in which amounts in which structural configurations, other than those exemplified and tested and found effective in the instant disclosure, would be within the genus of controlled release Tofacitinib compositions recited by the claims.

82. The Applicant has disclosed, in Examples 15-18, the testing of specific embodiments of the invention with respect to various pharmacokinetic parameters as a measure to ascertain if the different dosage forms exhibit any pharmacokinetic property as is desired. Specifically, Examples 15-18 involve testing the sustained release dosage forms as follows:

- Example 15 tests the bilayer osmotic capsules;

- Example 16 tests the matrix tablets;
- Example 17 tests the extrudable core system tablets;
- Example 18 also tests an extrudable core system tablet prepared according to the directions disclosed therein.

83. A person of average skill in the art would have to engage in extensive undue experimentation, conducting a myriad number of experiments to determine which oral dosage forms of Tofacitinib, comprising which ingredients (e.g., excipients, matrix polymers, osmotic agents, and coating polymers) in what amounts and in which configurations (e.g., osmotic forms, coated multiparticulate forms, matrix forms, shell/core forms), would achieve the pharmacokinetic parameters that are recited by the claims.

84. Therefore, the specification does not enable a person of average skill in the art to make or use the invention as claimed without undue experimentation. Consequently, the specification as filed does not provide enabling disclosure of the claims at hand.

85. The specification as filed fails to specifically disclose the compositions within the broad disclosure of the impugned specification that would possess the pharmacokinetic parameters recited by the claims. In light of said lack of specific disclosure the scope of claims is too broad and presently pending claims cover even dosage forms which are not contemplated in the specification.

86. The specification as filed also fails to disclose any correlation between the structure of the composition ingredients that could make up the core and the semi-permeable membrane coating. In absence of this information a person of average skill in the art has to undergo undue experimentation to determine which ingredients could be used to

formulate a composition within the scope of the claims having the recited pharmacokinetic parameters.

87. The amended claims of the impugned application recite a "semi-permeable membrane coating." However, there is no clarity as to the configuration of the coating in the dosage form. Specifically, there is no clarity about: a) onto what structural element is the coating coated, b) what is the combination of polymers, c) ratio/percentage of the polymers, d) other ingredients, e) the ratio/percentage of these other ingredients, and f) thickness of this semi-permeable membrane? In light of same presently pending claims of the impugned application are indefinite.

88. Therefore, the currently pending claims lack clarity, are indefinite claims the scope of the claims is too broad, there is a lack of correlation between structure and function of the claimed dosage forms, the specification does not to disclose a representative number of species which describe the claimed genus, and a person off average skill in the art would have to undergo undue experimentation to arrive at the claimed invention.

89. The impugned patent application does not provide adequate teaching to a person of average skill in the art to practice the invention. Considering above, impugned application does not sufficiently and clearly describe the invention. Therefore, the impugned application should be refused on this ground alone.

GROUND 5 -Section 25(1)(h)

90. The Applicant has failed to disclose to the Patent Office the information required under Section 8. The Applicant is required to provide all the information regarding the prosecution of the equivalent applications till the grant of the Indian

application to the Patent Office in writing from time to time and also within the prescribed time.

91. It is observed that Applicant has not provided information about updated the status of corresponding application in the Form-3 which information has not been provided to the learned Controller.

92. It is submitted that the Applicant has failed to disclose the details of corresponding foreign applications and impugned patent application to be refused.

93. Therefore, the applicant has failed to comply with the requirements of the section 8 of the act and the opponent demands rejection on this ground also.

94. The opponents crave leave to file further submissions and evidence with respect to this ground.

CONCLUSION

95. In view of the above, the claims are not novel, inventive and not patentable and insufficient. The pre-grant opposition as filed may be allowed and the subject patent application may be refused.

HEARING REQUESTED

96. The Opponent hereby requests a hearing under section 25(1) of the Patents Act, 1970 (hereinafter referred to as “the Patents Act”) and Rule 55 of the Patents Rules (hereinafter referred to as “the Rules”).

P R A Y E R

In the fact and circumstances of the case, the Opponent prays as follows:

- i. that the Controller take the present Opposition on record; that the Indian application 8222/DELNP/2015, be rejected under Section 25(1) of the Patents (Amendment) Act, 2005;
- ii. that the Opponent may be allowed to file further documents and evidence if necessary to support their averments;
- iii. that the Opponent may be allowed to file rejoinder and affidavit if necessary to support their averments;
- iv. that the Opponent may be granted an opportunity of being heard in the matter before any final orders are passed;
- v. that the Opponent may be allowed to make further submissions in case the Patentee makes any amendments in the claims;
- vi. any other reliefs considering the facts and circumstances may be granted in favour of the Opponent in the interest of justice.

Dated this 27th day of December 2021



RAJESHWARI H. IN/PA – 0358
OF RAJESHWARI AND ASSOCIATES
AGENT FOR THE OPPONENT

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE, NEW DELHI

Annexure - 1

I/We Claim:

1. A once daily pharmaceutical dosage form comprising a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen, and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer, wherein said dosage form is a sustained release dosage form, and when added to a test medium comprising 900 ml of 0.05M pH 6.8 potassium phosphate buffer at 37° C in a standard USP rotating paddle apparatus and the paddles are rotated at 50 rpm, dissolves not more than 30% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 1 hour, and not less than 35% and not more than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 2.5 hours and not less than 75% of the tofacitinib, or pharmaceutically acceptable salt thereof, in 5 hours and wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to a subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib, or pharmaceutically acceptable salt thereof.

2. A once daily pharmaceutical dosage form comprising a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen, and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer, wherein the dosage form is a sustained release dosage form and when administered orally to a subject provides an AUC in the range of 80% to 125% of the AUC of 5 mg of tofacitinib or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof administered as an immediate release formulation BID and provides a ratio of geometric mean plasma C_{max} to C_{min} from about 10 to about 100 and wherein the dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to the subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib or pharmaceutically acceptable sat thereof.

3. The pharmaceutical dosage form of claim 2, wherein the AUC range is 90% to 110% and the geometric mean plasma concentration C_{max} to C_{min} from about 20 to about 40.

4. The pharmaceutical dosage form of claim 3, wherein the geometric mean plasma concentration C_{max} to C_{min} from about 20 to about 30.

5. The pharmaceutical dosage form of claim 2, wherein when the dosage form is administered orally to the subject provides a mean plasma C_{max} in the range of 70% to 125% of the mean plasma C_{max} of tofacitinib administered as the immediate release formulation BID at steady state.

6. The pharmaceutical dosage form of claim 2, wherein when the dosage form is administered orally to the subject provides a drug holiday in the range of 80% to 110% of the drug holiday of tofacitinib administered as the immediate release formulation BID over a 24 hour period.

7. The pharmaceutical dosage form of claim 2, having a drug holiday from about 15 to about 18 hours over the 24 hour period.

8. A once daily pharmaceutical dosage form comprising

a core comprising 11 mg of tofacitinib, or an equivalent amount of tofacitinib in the form of a pharmaceutically acceptable salt thereof, and an osmagen,

and a semi-permeable membrane coating surrounding the core wherein said coating comprises a water-insoluble polymer,

wherein said dosage form is a sustained release dosage form, and when administered to a subject has a mean area under the plasma concentration versus time curve following administration from about 17 ng-hr/mL per mg of tofacitinib dosed to about 42 ng-hr/mL per mg of tofacitinib dosed and a ratio of geometric mean plasma C_{max} to C_{min} from about 10 to about 100 and wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, to the subject primarily by osmotic pressure and wherein the water-insoluble polymer is a cellulose derivative that sustains release of the tofacitinib or pharmaceutically acceptable salt thereof.

9. The pharmaceutical dosage form of claim 8, wherein the ratio of geometric mean plasma C_{max} to C_{min} from about 20 to about 40.

10. The pharmaceutical dosage form of claim 9, wherein the ratio of geometric mean plasma C_{max} to C_{min} from about 20 to about 30.

11. The pharmaceutical dosage form of claim 8, wherein the subject has a single, continuous time above about 17 ng/ml from about 6 to about 15 hours and a single, continuous time below about 17 ng/ml from about 9 to about 18 hours over a dosing 24 hours interval.

12. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time above about 17 ng/ml from about 6 to about 9 hours.
13. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time below about 17 ng/ml from about 15 to about 18 hours.
14. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time above about 17 ng/ml from about 11 to about 15 hours.
15. The pharmaceutical dosage form of claim 11, wherein the subject has a single, continuous time below about 17 ng/ml from about 9 to about 13 hours.
16. The pharmaceutical dosage form of claim 8, wherein the subject has a mean maximum plasma concentration (C_{max}) from about 3 ng/mL per mg to about 6 ng/mL per mg of tofacitinib dosed.
17. The pharmaceutical dosage form of claim 8, wherein said dosage form delivers the tofacitinib, or pharmaceutically acceptable salt thereof, by a system selected from the group consisting of an extrudable core system, a swellable core system, and an asymmetric membrane technology.
18. The pharmaceutical dosage form of claim 8 wherein, said cellulose derivative is cellulose acetate.
19. The pharmaceutical dosage form of claim 8, wherein said coating further comprising a water soluble polymer having an average molecular weight between 2000 and 100,000 daltons.
20. The pharmaceutical dosage form of claim 19, wherein said water soluble polymer is selected from the group consisting of water soluble cellulose derivatives, acacia, dextrin, guar gum, maltodextrin, sodium alginate, starch, polyacrylates, and polyvinyl alcohols.
21. The pharmaceutical dosage form of claim 20, wherein said water soluble cellulose derivatives comprises hydroxypropylcellulose, hydroxypropylmethylcellulose or hydroxyethylcellulose.
22. The pharmaceutical dosage forms of claim 8, wherein the osmagen is a sugar.
23. The pharmaceutical dosage form of claim 22, wherein the sugar is sorbitol.
24. The once daily pharmaceutical dosage form of claim 8 wherein the subject has a mean steady-state minimum plasma concentration (C_{min}) less than about 0.3 ng/mL per mg of tofacitinib dosed.

25. The once daily pharmaceutical dosage form of claim 8, wherein when administered orally to the subject has a mean fed/fasted ratio of the area under the plasma concentration versus time curve from about 0.7 to about 1.4 and a mean fed/fasted ratio of the maximum plasma concentration (C_{max}) from about 0.7 to about 1.4.

Dated **September 10, 2015**

MALATHI LAKSHMIKUMARAN
IN/PA -1433
OF LAKSHMIKUMARAN & SRIDHARAN
AGENT FOR THE APPLICANT

To
The Controller of Patents
The Patent Office, at Delhi

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
2 August 2012 (02.08.2012)

(10) International Publication Number
WO 2012/100949 A1

(51) International Patent Classification:

A61K 31/515 (2006.01) **A61K 9/28** (2006.01)
A61K 9/20 (2006.01) **A61K 9/22** (2006.01)

(21) International Application Number:

PCT/EP2012/000353

(22) International Filing Date:

26 January 2012 (26.01.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

11000677.2 27 January 2011 (27.01.2011) EP

(71) Applicant (for all designated States except US): **RATIO-
PHARM GMBH** [DE/DE]; Graf-Arco-str. 3, 89079 Ulm
(DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **STEFAN, Ralph**
[DE/DE]; Kirchstrasse 28, 88370 Ebenweiler (DE). **SIEV-
ERT, Frank** [DE/DE]; Lichseweg 27, 89604 Allmendingen
(DE).

(74) Agent: **AECHTER, Bernd**; Ter Meer Steinmeister & Partner
GBR, Mauerkircherstrasse 45, 81679 Munchen (DE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: ORAL DOSAGE FORMS FOR MODIFIED RELEASE COMPRISING TASOCITINIB

(57) Abstract: The invention essentially relates to oral dosage forms comprising a JAK3 inhibitor, preferably tasocitinib, suitable for modified release, and processes of preparing such oral dosage forms.



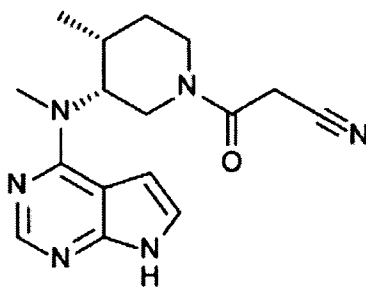
WO 2012/100949 A1

ORAL DOSAGE FORMS FOR MODIFIED RELEASE COMPRISING TASOCITINIB

Background

The invention essentially relates to oral dosage forms comprising a pharmaceutically active substance, preferably 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)3-oxo-propionitrile, suitable for modified release, and processes of preparing such oral dosage forms.

3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)3-oxo-propionitrile apparently has the chemical formula $C_{16}H_{20}N_6O$ and is reported in WO 03/048126 as an inhibitor of protein kinases, such as the enzyme Janus Kinase 3 (hereinafter also referred to as "JAK3") and as such it has been asserted that it is useful in therapy as immunosuppressive agents for organ transplants, xeno transplantation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other indications, where immunosuppression would be desirable (see WO 03/048126), and is known under the INN tasocitinib, which has recently changed to tofacitinib. The 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)3-oxo-propionitrile apparently has the chemical structure of formula (I):



formula (I).

In this regard it is noted that the compound according to formula (I) would seem to refer to 3-((3R,4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl)3-oxo propionitrile (= tasocitinib) or its solvates or hydrates as well as pharmaceutical acceptable salts thereof are said to be obtained according to the

procedures as outlined in WO 02/096909. The mono citrate form has apparently been described in WO 03/048162.

Whereas the prior art (WO 03/048162, WO 02/096909) mentions that tasocitinib might be formulated into pharmaceutical compositions, no specific formulations have been disclosed.

When formulating tasocitinib, various physiological factors such as gastrointestinal pH, enzyme activities, gastric and intestinal transit rates apparently negatively influenced important parameters of tasocitinib. As a solution for this problem an immediate release formulation, prepared by dry-compaction, was suggested, since the known pharmacokinetic parameters of tasocitinib taught the skilled person that an immediate release dosage form would be beneficial. In addition it was reported that especially low dose tasocitinib formulations generally suffered from the difficulty of providing a sufficient content uniformity.

Hence, there is a need for the provision of pharmaceutical dosage forms and processes for the manufacture of these pharmaceutical dosage forms comprising tasocitinib, which do not suffer from the above mentioned draw-backs. Preferably, an oral dosage form should be provided having improved properties like content-uniformity, solubility, dissolution profile, well defined, predictable and reproducible dissolution rates, stability and bioavailability. Such an oral dosage form should be producible in a large scale in an economic beneficial way.

Summary of the Invention

The present invention provides an oral dosage form for modified release that can overcome the above drawbacks, the oral dosage form for modified release comprising

- (a) tasocitinib (= tofacitinib), and
- (b) a non-erodible material.

It was found that the dosage forms of the present invention despite the high solubility of tasocitinib have the advantage that the tasocitinib is gradually released over a relatively long period so that the drug is maintained in the blood stream for a long time and at a uniform concentration. This allows administration, e.g., only once daily. Administration

of the oral dosage forms of the present invention result in little blood level fluctuation, that means periods of transient therapeutic overdose, followed by a period of therapeutic underdosing can be avoided. Consequently, the dosage forms of the present invention, particularly provide a constant release of tasocitinib, preferably over
5 a prolonged period of time, which avoids blood level fluctuations of the drug in the patient.

Moreover, the dosage form of the present invention is released in the gastrointestinal tract of the patient but not in the stomach, in order to avoid a "nervous stomach" or
10 nausea.

A further subject of the present invention is a process for manufacturing the oral dosage forms of the present invention, preferably in form of a modified release tablet.

15 Detailed Description of the Invention

In the following, explanations regarding the pharmaceutical dosage form of the present invention are given. However, these explanations also apply to the processes for manufacturing the pharmaceutical dosage form, such as the modified release tablet of
20 the present invention, and to the use of the present invention.

Within the present application generally the term "modified release" is used as defined by the USP. Preferably, modified release dosage forms are those whose drug release characteristics accomplish therapeutic or convenience objectives not offered by
25 immediate release forms. Generally, immediate release (IR) forms release at least 70 % of the drug within 1 hour or less. The term "modified release" can comprise delayed release, prolonged release, sustained release, extended release and/or controlled release.

30 Delayed release usually indicates that the drug (i.e., tasocitinib) is not being released immediately after administration but at a later time, preferably less than 10 % are released within two hours after administration.

Prolonged release usually indicates that the drug (i.e., tasocitinib) is provided for absorption over a longer period of time than IR forms, preferably for about 2 to 24 hours, in particular for 3 to 12 hours.

- 5 Sustained release usually indicates an initial release of drug (i.e., tasocitinib), sufficient to provide a therapeutic dose soon after administration, preferably within two hours after administration, and then a gradual release after an extended period of time, preferably for about 3 to 18 hours, in particular for 4 to 8 hours.
- 10 Extended release usually indicates a slow drug (i.e., tasocitinib) release, so that plasma concentrations are maintained at a therapeutic level for a time period of between 6 and 36 hours, preferably between 8 and 24 hours.

- Controlled release dosage forms usually release the drug (i.e., tasocitinib) at a
- 15 constant rate and provide plasma concentrations that remain essentially invariant with time.

- In a preferred embodiment, the oral dosage form of the present invention is an extended release dosage form.

- 20 In particular, the oral dosage form of the present invention shows a drug release of less than 10 % within 2.0 hours. Further, the oral dosage form of the present invention shows a drug release of more than 80 % within 3.0 to 12.0 hours, preferably between 4.0 and 8.0 hours.

- 25 Generally, within this application the release profile is determined according to USP 31-NF26 release method, apparatus II (paddle). The measurements are carried out in preferably 900 ml 0.1 n HCl at 37 °C, wherein the stirring speed was 75 rpm, and re-buffering after 2 hours to pH 6.8.

- 30 In a preferred embodiment, the oral dosage form of the present invention is a solid oral dosage form, in particular a solid peroral dosage form.

- The term tasocitinib (component (a)) as used in the present invention relates to the
- 35 compound as shown in formula I (free base) or to its acid form or its basic form. That

means, "tasocitinib" as used in the present invention also relates to the pharmaceutically acceptable salts, preferably pharmaceutically acceptable acid addition salts, e.g., as described in WO 02/096909. The acids, which are used to prepare the pharmaceutically acceptable acid addition salts, are preferably those which

5 form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate (preferably monotartrate and bitartrate), succinate, malate (preferably monomalate), maleate, oxalate (preferably monooxalate), fumarate, gluconate, saccharate, benzoate,

10 methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The term "tasocitinib" also relates to stereospecific base addition salts of formula (I). The chemical bases that may be used as reagents to prepare pharmaceutically

15 acceptable base salts of those compounds of formula I that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to, those derived from such pharmacologically acceptable cations, such as alkali metal cations (e.g., potassium and sodium) and alkaline earth metal cations (e.g., calcium and magnesium), ammonium or water soluble amine

20 addition salts, such as N-methylglucamine-(meglumine), and the lower alkanol ammonium and other base salts of pharmaceutically acceptable organic amines.

In the oral dosage form of the present invention, tasocitinib as the active ingredient (component (a)) can be provided in amorphous form, preferably as amorphous

25 tasocitinib citrate, in crystalline form or as a mixture of both forms. Preferably, tasocitinib is present in crystalline form, wherein the crystalline modification is as described in WO 03/048162. In a particularly preferred embodiment of the present invention tasocitinib is provided as the citrate or hemi citrate. Most preferred is the crystalline form of the citrate or hemi citrate of tasocitinib.

30 In a preferred embodiment, the oral dosage form of the present invention comprises 1.0 to 60 wt.%, more preferably 2.0 to 30 wt.-%, still more preferably 3.0 to 20 wt.%, in particular 4.0 to 15 wt.% tasocitinib, based upon the total weight of the oral dosage form and based on the weight of tasocitinib in form of the free base, i.e. as shown in

35 formula (I) above.

In a preferred embodiment, the oral dosage form of the present invention comprises 1.0 to 100 mg, more preferably 2.0 to 50 mg, still more preferably 3.0 to 20 mg, in particular 4.0 to 12 mg tasocitinib, based upon the total weight of the oral dosage form and based on the weight of tasocitinib in form of the free base, i.e. as shown in formula

5 (I) above.

In a preferred embodiment, the pharmaceutical composition of the invention can comprise only tasocitinib as pharmaceutical active agent.

10 In another preferred embodiment the pharmaceutical composition of the invention can comprise tasocitinib in combination with further pharmaceutical active agent(s).

15 It is preferred that the pharmaceutical composition of the invention comprises only tasocitinib as pharmaceutical active agent.

The modified release tablet of the present invention further contains a non-erodible material (b). Generally, the non-erodible material is suitable as release controlling agent.

20

In a first embodiment, the non-erodible material can be described as providing a scaffold (matrix) for embedding the active ingredient and to form a physical barrier, which hinders the active ingredient from being released immediately from the dosage form. Thus, the non-erodible material has the effect that the active ingredient can be
25 released from the scaffold in continuous manner. Release of the drug from the matrix can further be by dissolution controlled as well as diffusion controlled mechanisms. In this first embodiment the non-erodible material functions as matrix forming material.

30 In a second embodiment, the non-erodible material can be described as a shell-forming material. Preferably, in that embodiment the oral dosage form is a tablet. The release modifying shell preferably encompasses the drug containing tablet core.

In a third embodiment, the non-erodible material can be described as a release modifying coating in a multiple unit pellet system (MUPS).

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Generally, (i.e. for all three above described embodiments) the oral dosage form of the present invention further comprises a non-erodible material (b). Non-erodible materials are materials, which are able to provide modified release properties, preferably due to their limited solubility, more preferably due to their limited solubility in aqueous conditions at pH 5.0. Preferably, the non-erodible polymer has a water solubility of less than 33 mg/l at a temperature of 25 °C at a pH of 5.0, more preferably of less than 22 mg/l, still more preferably of less than 11 mg/l, especially from 0.01 to 5 mg/l. The water-solubility is determined according to the column elution method of the Dangerous Substances Directive (67/548/EEC), Annex V, Chapter A6. The pH value is determined according to Ph.Eur. 6.0, 2.2.3. The pH value of the aqueous medium usually is achieved by addition of HCl (or NaOH), if necessary.

The solubility of the non-erodible material can be pH independent or pH dependent. Both embodiments are preferred. If the non-erodible material is pH dependent, it is preferred that the non-erodible material has a solubility in water at 25 °C at a pH of 7.0 of more than 33 g/l, more preferably of 50 g/l to 10,000 g/l, still more preferably from 100 g/l to 5,000 g/l, in particular from 200 g/l to 2,000 g/l.

The non-erodible material can comprise an inert non-erodible material, a lipid non-erodible material and/or a hydrophilic non-erodible material. Examples for an inert non-erodible material are ethylcellulose, methacrylate copolymer, polyamide, polyethylene, and polyvinyl acetate; examples for lipid non-erodible materials are carnauba wax, cetyl alcohol, hydrogenated vegetable oils, microcrystalline waxes, monoglycerides, triglycerides and PEG monostearate; examples for hydrophilic non-erodible materials are alginates, carbopol, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, xanthan gum and polyethylene oxide as well as mixtures thereof..

In a preferred embodiment, the non-erodible material is a non-erodible polymer. The non-erodible polymer usually has a weight average molecular weight ranging from 30,000 to 3,000,000 g/mol, preferably from more than 50,000 to 2,500,000 g/mol, more preferably from more than 125,000 to 2,000,000 g/mol, still more preferably from 250,000 to 2,200,000 g/mol, particularly preferred from 400,000 to 1,500,000 g/mol. Furthermore, a 2 % w/w solution of the non-erodible polymer in water at pH 7.0 preferably has a viscosity of more than 2 mPas, more preferably of more than 5 mPas,

particularly more than 8 mPas and up to 850 mPas, when measured at 25 °C. The viscosity is determined according to Ph. Eur., 6th edition, Chapter 2.2.10. In the above definition the term "solution" may also refer to a partial solution (in case that the polymer does not dissolve completely in the solution). The weight average molecular weight is preferably determined by gel electrophoresis.

It is further preferred that the non-erodible polymer has a melting temperature of below 220 °C, more preferably of between 25 °C and 200 °C. In a particularly preferred embodiment the melting temperature is between 35 °C and 190 °C. The determination of the melting temperature is carried out according to Ph. Eur., 6th edition, Chapter 2.2.15.

If the non-erodible material (b) is a polymeric material, it preferably can be selected from acrylic polymers or acrylic copolymers such as polymers obtained from acrylic acid and/or methacrylic acid monomers. Other preferred polymers include, but are not limited to, cellulose and cellulose derivatives such as cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl methyl cellulose acetate (HPMCA), hydroxypropyl methyl cellulose phthalate (HPMCP) and cellulose acetate succinate (CAS), polyvinyl polymers such as polyvinyl alcohol phthalate, polyvinyl acetate phthalate and polyvinyl butyl phthalate, and mixtures of one or more of these polymers.

In particular, the following kinds of non-erodible polymers are particularly preferred.

1. Cellulose ether, preferably ethyl cellulose, preferably ethyl cellulose having an average molecular weight of 150,000 to 300,000 g/mol and/or an average degree of substitution, ranging from 1.8 to 3.0, preferably from 2.2 to 2.6. This embodiment preferably is used for MUPS or core/shell-tablets;

2. Cellulose ester, preferably cellulose acetate phthalate, carboxymethyl ethyl cellulose, hydroxypropyl methylcellulose phthalate. This embodiment is preferably used for core/shell tablets;

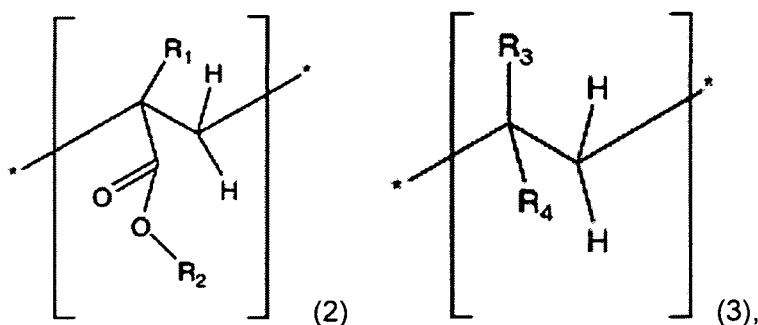
3. Copolymers of methacrylic acid or methacrylic acid esters, preferably ethylacrylate-methyl methacrylate and methacrylic acid-methyl methacrylate. Particularly preferred is

ethylacrylate-methylmethacrylate-trimethylammonioethylmethacrylate-chloride, for example Eudragit[®] RL PO (Rohm) and Eudragit[®] RS PO (Rohm).

4. Polyvinyl acetate or polyvinyl acetate copolymers, preferably polyvinyl acetate phthalate; and mixtures thereof.

Preferred acrylic polymers are, for example, polyacrylate, polymethacrylate as well as derivatives and mixtures or copolymers thereof. The polyacrylates used in the invention preferably show the above indicated parameters (e.g. weight average molecular weight, solubility, etc).

In a preferred embodiment the non-erodible acrylic polymer (b) is a polymer consisting of the structures according to the general formulae (2) and (3).



wherein in formulae (2) and (3)

R_1 is a hydrogen atom or an alkyl group, preferably a hydrogen atom or a methyl group or an ethyl group, particularly preferred a methyl group;

- 20 R_2 is a hydrogen atom or an alkyl group, preferably a hydrogen atom or a C_1 - C_4 alkyl group, particularly preferred a methyl group, ethyl group or butyl;

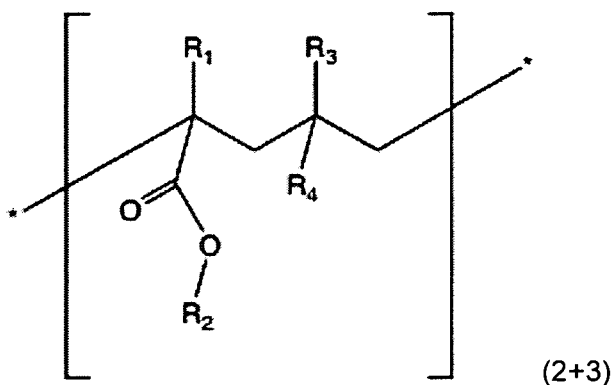
R_3 is a hydrogen atom or an alkyl group, preferably a hydrogen atom or a methyl group;

- 25 R_4 is an organic group, preferably a carboxylic acid or a derivative thereof, particularly preferred a group according to the formula $-COOH$, $-COOR_5$,

R_5 is an alkyl group or a substituted alkyl group, preferably a methyl, ethyl, propyl or butyl group, or $-CH_2-CH_2-N(CH_3)_2$ or $-CH_2-CH_2-N(CH_3)_3^+$ halogen⁻ (in particular Cl^-) as substituted alkyl group.

The acrylic polymer (b) according to formulae (2) and (3) is usually comprised of structures with a molar ratio of from 1 : 40 to 40 : 1. The preferred ratio of the structures of formula (2) to structures of formula (3) is from 2 : 1 to 1 : 1, particularly 1 : 1. When R_4 is $-\text{COO}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_3^+\text{Cl}^-$, the ratio of structures according to formula (2) to structures of formula (3) preferably is 20 : 1 to 40 : 1.

In case of an alternating copolymerization with a ratio of 1 : 1, this results in a preferred polymer according to formula (2+3)



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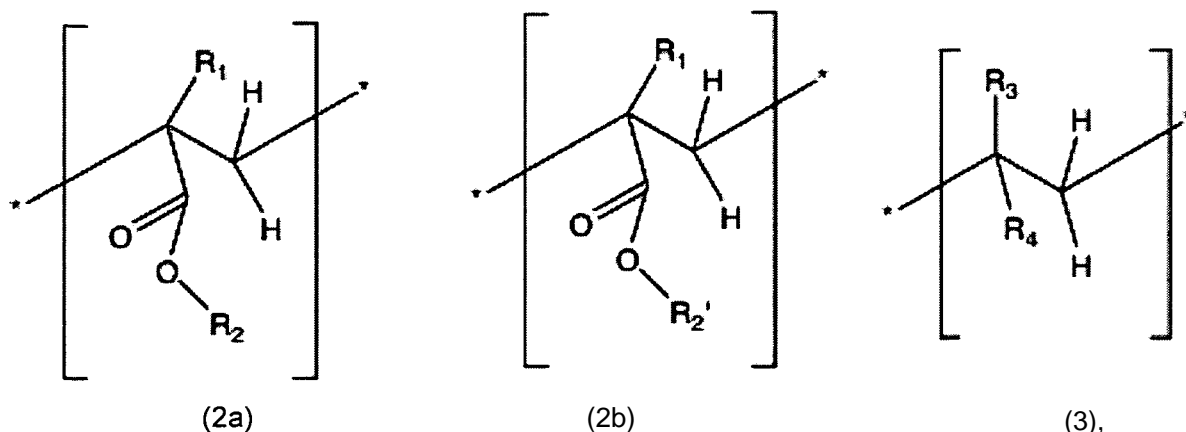
Polyacrylates according to the formulae (2) and (3) as mentioned above are particularly preferred, wherein R_1 and R_3 are alkyl, particularly methyl, R_2 is methyl and/or ethyl and R_4 is hydrogen or $-\text{COO}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_3^+\text{Cl}^-$. A particularly preferred ratio of the structures according to formula (2) to the structures according to formula (3) is 1 : 1 or 1 : 20. A corresponding polymer preferably has a weight average molecular weight of from 20,000 to 250,000 g/mol, more preferred of from 30,000 to 180,000 g/mol.

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In a particularly preferred embodiment in formula (2) (or in formula (2+3) as well), as indicated above, R_2 is both a methyl and a butyl group, whereby the ratio methyl to butyl group preferably is 1 : 1.

20

Further, the acrylic polymer preferably can be a ternary polymer comprising the structures according to the general formulae (2a), (2b) and (3)



wherein R_1 and R_3 are hydrogen or alkyl, particularly methyl, R_2 is methyl, R_2' is ethyl and R_4 is $-\text{COO}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_3^+\text{Cr}$.

Further, a preferred non-erodible polymer is a blend of lactose and hydroxypropylmethylcellulose (hypromellose), more preferably a spray agglomerated blend, in particular of 50 parts lactosemonohydrate and 50 parts hypromellose.

The non-erodible material (b) is contained in the tablet in an amount of 5 to 80 wt.%, preferably from 10 to 50 wt.%, most preferably from 15 to 40 wt.%, based upon the total weight of the oral dosage form. If too little non-erodible material is used, the formulations may break up during the passage down the gastrointestinal tract and this, in turn, may lead to a premature release of a large portion of the content of the drug. If too much matrix former is used, there is a risk that some of the drug will be encapsulated and not released from the tablet.

The oral dosage form of the invention further optionally comprises a pore-forming material (c). The term "channelling agent" is in the art often synonymously used for the pore-forming material of the present invention. Since the pore-forming material is generally soluble in the gastrointestinal tract and leaches out from the oral dosage form, the pore-forming material can be described as having the effect of forming pores, such as small holes within the tablet, through which the active ingredient can be released from the tablet matrix in a controlled manner. Thus, release of the active ingredient generally depends on dissolving the pore forming material and thereby forming a porous matrix of capillaries such that the drug can leach out of the matrix.

The pore-forming substance usually has a water solubility of more than 50 mg/l, preferably more than 100 mg/l, at a temperature of 25 °C and pH 5.0, more preferred of more than 250 mg/l and particularly preferred of more than 25 g/l. The water-solubility of the pore-forming substance may range up to 2.5 kg/l. The water-solubility is determined according to the column elution method of the Dangerous Substances Directive (67/548/EEC), Annex V, Chapter A6.

The pore-forming substances can be selected from inorganic substances, preferably from inorganic salts such as NaCl, KCl, Na₂SO₄. Furthermore, the pore-forming substances can be selected from organic substances, in particular from organic substances being solid at 30 °C and having the above-mentioned water solubility. Suitable examples are PEG, particularly PEG, having a weight average molecular weight of from 2,000 to 10,000 g/mol.

Furthermore, polyvinylpyrrolidone, preferably having a weight average molecular weight of from 5,000 to 29,000 g/mol, PEG with a weight average molecular weight of 380 - 4800, polyethylene oxide with a weight average molecular weight of less than 100,000 and a viscosity of less than 20 mPa*s, sugar alcohols like mannitol, sorbitol, xylitol, isomalt, and mono or disaccharides, like lactose, are also suitable as pore-forming substances.

The pore forming material is usually contained in the tablet in an amount of 1 to 50 wt.%, preferably from 2 to 40 wt.%, most preferably from 5 to 30 wt.%, based upon the total weight of the oral dosage form.

The tablet of the present invention can further comprise at least one excipient (d) selected from solubilizers (d1), fillers (d2), disintegrants (d3), lubricants (d4), surfactants (d5), glidants (d6), anti-sticking agents (d7), plasticizers (d8) and mixtures thereof.

The composition of the subject invention preferably comprises one or more solubilizers, preferably hydrophilic solubilizers. Generally, the term "solubilizer" means any organic excipient, which is capable of improving the solubility and/or dissolution of the active pharmaceutical ingredient. Generally, the term "hydrophilic solubilizer" means any organic excipient, which possesses hydrophilic groups and is capable of improving the

solubility and/or dissolution of the active pharmaceutical ingredient. Preferably, the hydrophilic solubilizer is capable of reducing the dissolution time of a pharmaceutical composition by 5 %, more preferably by 20 %, according to USP 31-NF26 release method, using apparatus 2 (paddle), compared to the same pharmaceutical composition comprising calcium hydrogen phosphate instead of the hydrophilic solubilizer.

The solubilizers are selected, for example, from the group of known inorganic or organic excipients. Such excipients preferably include polymers, low molecular weight oligomers and natural products.

Preferably, the hydrophilic solubilizer is a water-soluble compound, having a water solubility of more than 10 mg/l, more preferably of more than 20 mg/l, still more preferably of more than 50 mg/l at a temperature of 25 °C. The solubility of the hydrophilic solubilizer might be e.g. up to 1,000 mg/l or up to 300 mg/ml at a temperature of 25 °C. The water-solubility is determined according to the column elution method of the Dangerous Substances Directive (67/548/EEC), Annex V, Chapter A6.

In a preferred embodiment the solubilizer is a hydrophilic polymer, preferably having the above-mentioned water-solubility. Generally, the term "hydrophilic polymer" encompasses polymers comprising polar groups. Examples for polar groups are hydroxy, amino, amido, carboxy, carbonyl, ether, ester and sulfonate. Amido groups are particularly preferred.

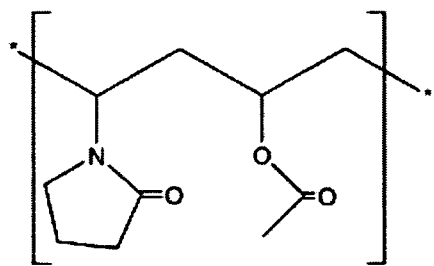
The hydrophilic polymer usually has a weight average molecular weight, ranging from 1,000 to 250,000 g/mol, preferably from 2,000 to 100,000 g/mol, particularly from 4,000 to 75,000 g/mol. Furthermore, a 2 % w/w solution of the hydrophilic polymer in pure water preferably has a viscosity of from 1 to 20 mPa*s, more preferably from 2 to 8 mPa*s at 25 °C. The viscosity is determined according to the European Pharmacopoeia (hereinafter referred to as Ph. Eur.), 6th edition, Chapter 2.2.10.

Furthermore, the hydrophilic polymer used as hydrophilic solubilizer preferably has a glass transition temperature (T_g) or a melting point of 25 °C to 200 °C, more preferably of 90 °C to 170 °C. The glass transition temperature, T_g , is the temperature, at which the hydrophilic polymer becomes brittle on cooling and soft on heating. That means,

above T_g , the hydrophilic polymers become soft and capable of plastic deformation without fracture. The glass transition temperature or the melting point are determined with a Mettler-Toledo® DSC 1, wherein a heating rate of 10 °C per minute and a cooling rate of 15 °C per minute is applied. The determination method essentially is based on Ph. Eur. 6.1, section 2.2.34. For the determination of T_g , the polymer is heated twice (i.e. heated, cooled, heated).

More preferably, derivatives of cellulose (e.g. hydroxypropyl methyl cellulose (HPMC), preferably having a weight average molecular weight from 20,000 to 90,000 g/mol, and/or preferably a ratio of methyl groups from 10 to 35 %, and preferably a ratio of hydroxypropyl groups from 1 to 35 %; hydroxypropyl cellulose (HPC), preferably having a weight average molecular weight of from 40,000 to 100,000 g/mol), polyvinylpyrrolidone, preferably having a weight average molecular weight of from 10,000 to 60,000 g/mol, copolymers of polyvinylpyrrolidones, preferably copolymers comprising vinylpyrrolidone and vinylacetate units (e.g. Povidon® VA 64; BASF), preferably having a weight average molecular weight of 40,000 to 75,000 g/mol, polyoxyethylene alkyl ethers, co-blockpolymers of ethylene oxide and propylene oxide, preferably having a polyethylene content of 70 to 90 wt.% and/or preferably having a weight average molecular weight from 1,000 to 50,000 g/mol, in particular from 3,000 to 25,000 g/mol, polyvinyl alcohol, polyethylene glycol, preferably having a weight average molecular weight ranging from 1,000 to 50,000 g/mol, are used as hydrophilic solubilizers. The weight average molecular weight is preferably determined by gel electrophoresis.

In particular, polyvinylpyrrolidone and copolymers of polyvinylpyrrolidone, in particular copolymers comprising vinylpyrrolidone and vinylacetate units, having the structure



can be used as hydrophilic solubilizers.

It is particularly preferred that the above-mentioned kinds of hydrophilic polymers fulfill the functional requirements (molecular weight, viscosity, T_g , melting point, non-semi-permeable properties), as illustrated above.

- 5 In the pharmaceutical composition of the present invention, at least one of the above-mentioned hydrophilic solubilizers is present. Alternatively, a combination of two or more hydrophilic solubilizers can be employed.

10 Usually, solubilizers can be used in an amount of 0.1 to 20 wt.%, preferably of 1 to 15 wt.% based on the total weight of the oral dosage form.

Generally, fillers are used to top up the volume for an appropriate oral deliverable dose, when low concentrations of the active pharmaceutical ingredients (about 30 wt.% or lower) are present. Preferred fillers of the invention are calcium phosphate, saccharose, calcium carbonate, calcium silicate, magnesium carbonate, magnesium
15 oxide, maltodextrin, glucopyranosyl mannitol, calcium sulfate, dextrate, dextrin, dextrose, hydrogenated vegetable oil and/or cellulose derivatives, such as microcrystalline cellulose. A pharmaceutical composition according to the invention may comprise an inorganic salt as a filler. Preferably, this inorganic salt is dicalcium
20 phosphate, preferably in form of the dihydrate (dicalfos).

Dicalcium phosphate dihydrate is insoluble in water, non-hygroscopic, but still hydrophilic. Surprisingly, this behavior contributes to a high storage stability of the composition.

25 Usually, fillers can be used in an amount of 0 to 60 wt.%, preferably of 5 to 40 wt.%, based on the total weight of the composition.

The oral composition of the present invention can further comprise one or more of a disintegrant. In a preferred embodiment of the invention, the tablet does not contain a disintegrant.

30 Generally, disintegrants are compounds, capable of promoting the break up of a solid composition into smaller pieces when the composition gets in contact with a liquid, preferably water.

Preferred disintegrants are sodium carboxymethyl starch, cross-linked polyvinylpyrrolidone (crospovidone), sodium carboxymethyl glycolate (e.g. Explotab*), swelling polysaccharide, e.g. soya polysaccharide, carrageenan, agar, pectin, starch and derivatives thereof, protein, e.g. formaldehyde - casein, sodium bicarbonate or mixtures thereof. Crospovidone is particularly preferred as disintegrant. Furthermore, a combination of crospovidone and agar is particularly preferred.

Usually, disintegrants can be used in an amount of 0 to 20 wt.%, preferably of 1 to 10 wt.%, based on the total weight of the composition.

In a preferred embodiment of the present invention the oral dosage form is free of any disintegrants.

The oral dosage form of the present invention might further comprise one or more of a surfactant (d4). Preferably, sodium lauryl sulfate is used as surfactant.

Usually, surfactants can be used in an amount of 0.05 to 2 wt.%, preferably of 0.1 to 1.5 wt.%, based on the total weight of the oral dosage form.

Additionally, the oral dosage form of the present invention may comprise a lubricant (d5), a glidant (d6) and/or an anti-sticking agent (d7).

In a preferred embodiment of this invention, a lubricant may be used. Lubricants are generally employed to reduce dynamic friction. The lubricant preferably is a stearate, talcum powder or fatty acid, more preferably, hexanedioic acid or an earth alkali metal stearate, such as magnesium stearate. The lubricant is suitably present in an amount of 0.1 to 3 wt.%, preferably about 0.5 to 1.5 wt.% of the total weight of the composition. Preferably, the lubricant is applied in a final lubrication step during the powder preparation. The lubricant generally increases the powder flowability.

The glidant can for example be colloidal silicone dioxide (e.g. Aerosil®). Preferably, the glidant agent is present in an amount of 0 to 8 wt.%, more preferably at 0.1 to 3 wt.% of the total weight of the composition. Preferably, the silicone dioxide has a specific surface area of 50 to 400 m²/g, measured by gas adsorption according to Ph. Eur., 6th edition, Chapter 2.9.26. multipoint method, volumetric determination

The anti-sticking agent is for example talcum and may be present in amounts of 0.05 to 5 wt.%, more preferably in an amount of 0.5 to 3 wt.% of the total weight of the composition.

- 5 Furthermore, in a preferred embodiment the pharmaceutical composition of the present invention further comprises one or more plasticizers (d8). The "plasticizers" usually are compounds capable of lowering the glass transition temperature (T_g) of the non-erodible material, preferably the non-erodible polymer, preferably of lowering T_g from 1 to 50 °C, especially from 5 to 30 °C. Plasticizers (d8) usually are low molecular weight
10 compounds (having a molecular weight from 50 to 500 g/mol) and comprise at least one hydrophilic group.

Examples of suitable plasticizers are dibutyl sebacetate (DBS), Myvacet® (acetylated monoglycerides), triacetin (GTA), citric acid esters, like acetyltriethyl citrate (ATEC) or
15 triethyl citrate (TEC), propylene glycol, dibutyl phthalate, diethyl phthalate, or mixtures thereof.

The combined use of the non-erodible polymer (b) and the pore-forming substance (c) and optionally the plasticizer (d8) preferably is capable of modifying the drug release
20 rate. The use of plasticizers is particularly preferred in the third embodiment concerning MUPS.

Regarding the above mentioned pharmaceutically acceptable excipients, the application generally refers to "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und
25 angrenzende Gebiete", edited by H. P. Fiedler, 5th Edition, Editio Cantor Verlag, Aulendorf and earlier editions, and "Handbook of Pharmaceutical Excipients", third edition, edited by Arthur H. Kibbe, American Pharmaceutical Association, Washington, USA, and Pharmaceutical Press, London.

30 In the tablet according to the present invention the non-erodible material (b), the pore forming material (c) and/or the at least one excipient (d) preferably have a surface of 0.2 to 10 m²/g, preferably of 0.3 to 8 m²/g, most preferably of 0.4 to 5 m²/g, as measured by gas adsorption according to Ph. Eur., 6th edition, Chapter 2.9.26, multipoint method, volumetric determination.

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In the tablet of the invention the at least one non-erodible material (b), the pore forming material (c) and/or the excipient(s) generally show a plastic behavior, such as a ductile behaviour. This behavior can be described by the yield pressure of the material. The materials of components (a), (b) and/or (c) generally have a yield pressure of less than 150 MPa, preferably less than 100 MPa, most preferably of less than 75 MPa. If the yield pressure is above 150 MPa, the material is too brittle and causes difficulties in being compressed into a tablet, bearing the risk that the tablet breaks or crumbles. The yield pressure can be determined from a Heckel plot. According to Heckel, there is a linear relationship between the relative porosity (inverse density) of a powder and the applied pressure. The slope of the linear regression is the Heckel constant, a material dependent parameter inversely proportional to the mean yield pressure (the minimum pressure required to cause deformation of the material undergoing compression). Thus, the yield pressure is obtained by measuring the reciprocal value from the slope of the Heckel plot.

In this context it is generally noted that, due to the nature of pharmaceutical excipients, it cannot be excluded that a certain compound meets the functional requirements of more than one of the above mentioned excipient classes. However, in order to enable an unambiguous distinction and terminology in the present application, the same pharmaceutical compound can only be subsumed as one of the functional excipient classes presented above. For example, if microcrystalline cellulose is used as a filler, it cannot additionally classify as a disintegrant (although microcrystalline cellulose has some disintegrating properties).

As explained above, the present invention concerns three preferred embodiments of the solid oral dosage form. Hence, the present invention further relates to three preferred embodiments of a process for producing said oral dosage forms.

In the first preferred embodiment, the present invention concerns a matrix dosage form, preferably a matrix tablet. The matrix tablet preferably is produced by a process, comprising the steps of

(1-1) providing (and optionally blending) components (a), (b), optionally c), and optionally (d),

(1-11) optionally agglomerating the components of step (I) to yield granules,

(1-111) compressing the mixture resulting from step (I) or (II) into tablets; and
 (1-IV) optionally coating the tablets, preferably with a suitable film (e).

In this first preferred embodiment of the invention, the dosage form preferably
 5 comprises tasocitinib, a non-erodible material, a pore-forming material, a filler, a glidant
 and a lubricant. In a further preferred embodiment, the composition comprises from 5
 to 20 wt.% of tasocitinib, from 25 to 60 wt.% of non-erodible material, from 10 to
 40 wt.% of a pore-forming material, from 10 to 40 wt.% of a filler, from 1 to 10 wt.% of a
 glidant and from 1 to 10 wt.% of a lubricant, based upon the total weight of the dosage
 10 form.

In a second preferred embodiment of the invention, the oral dosage form is in form of a
 tablet, comprising a core and a shell, wherein the core comprises components (a) and
 optionally (c) and/or (d), and wherein the shell comprises components (b) and
 15 optionally (c) and/or (d).

The tablet of the invention preferably is produced by a process, comprising the steps of

- (2-I) mixing components (a) and optionally (c) and/or (d),
- 20 (2-II) optionally agglomerating the components of step (I) to yield granules,
- (2-III) compressing the mixture into tablets, and
- (2-IV) coating the tablets with a coating comprising components (b) and
 optionally (c) and/or (d).
- (2-V) Optionally, the resulting tablets can be film-coated with a suitable film (e).

The preferred processes of the first and second embodiment are described below in
 more detail.

In step (1-1) or (2-1) components (a), (b), (c) and/or (d) can be provided in micronized
 30 form. Micronization can be carried out by milling, such as in a air jet mill. Preferably,
 the mean particle size (D50) of tasocitinib (a) is from 20 to 120 μm , and from
 components (b), (c) and/or (d) it is from 30 to 150 μm .

Optionally, the ingredients of the tablet of the invention are blended in order to provide
 35 a formulation having a homogenous distribution of tasocitinib (a) within the formulation.

Blending can be carried out with conventional mixing devices, e.g. in a free-fall mixer like Turbula® T10B (Bachofen AG, Switzerland). Blending can be carried out e.g. for 1 minute to 30 minutes, preferably for 2 minutes to less than 10 minutes.

- 5 Generally, the step (1-11) or (2-11) of "agglomerating" components (a) to (d) (components (c) and (d) optional) refers to a process, wherein particles are attached to each other, thereby giving larger particles. The attachments may occur through physical forces, preferably van der Waals forces. The attachment of particles preferably does not occur through chemical reactions.

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Agglomeration (II) can be carried out in different devices. For example, agglomeration can be carried out by a granulation device, preferably by a dry granulation device. More preferably, agglomeration can be carried out by intensive blending. For example, agglomeration can be carried out by blending in a free-fall mixer or a container mixer.

- 15 An example for a suitable free fall mixer is Turbula® T10B (Bachofen AG, Switzerland). Generally, the blending is carried out for a time, being long enough for agglomeration to occur. Usually, blending is carried out for 10 minutes to 2 hours, preferably for 15 minutes to 60 minutes, more preferably from 20 minutes to 45 minutes.

- 20 In a possible embodiment the agglomeration step can be carried out as a dry-compaction step. In a preferred embodiment the dry-compaction step is carried out by roller compaction. Alternatively, e.g. slugging can be used. If roller compaction is applied, the compaction force usually ranges from 1 to 30 kN/cm, preferably from 2 to 20 kN/cm, more preferably from 2 to 10 kN/cm. The gap width of the roller compactor
- 25 usually is 0.8 to 5 mm, preferably 1 to 4 mm, more preferably 1.5 to 3.2 mm, especially 1.8 to 3.0 mm. After the compaction step, the received comprimate preferably is granulated. Preferably, the granulation step is carried out by an elevated sieving equipment, e.g. Comil* U5 (Quadro Engineering, USA). Alternatively, compaction and granulation can be carried out within one device.

30

In a preferred embodiment, the agglomeration step is carried as melt processing, in particular melt granulation. For this, the mixture of components (a), (b), optionally (c) and optionally (d) are molten. In a preferred embodiment the melting conditions can be preferably chosen such that they assure that tasocitinib is obtained in a non-crystalline

35

form.

The specific melting conditions can depend on compounds (a), (b), optionally (c) and optionally (d). Usually, temperatures from 40 °C to 200 °C, preferably from 60 °C to 180 °C are used. Preferably, tasocitinib (a), the non-erodible material (b) and the optional components (c) and (d) in their respective ratios may be chosen to achieve an eutectic mixture. In this way, the need of high temperatures for melting can be decreased.

In another embodiment, the cooling off step can be conducted under cooling conditions chosen such that non-crystalline tasocitinib remains in a non-crystalline form. Non-crystalline tasocitinib can be detected by XRD or DSC.

Further, the above molten mixture can be granulated, either in molten state or after having cooled off.

The melt processing can be carried out, for example, by an extrusion process. Hence, the melting step and the granulating step preferably can be regarded as melt-extrusion processes. Generally, the extrusion process should be capable of providing essentially spherical particles. Suitable extruders are, for example, screw-feed extruders (axial or endplate, dome and radial) or gravity extruders (cylinder roll, gear roll or radial). Screw-feed extruders are preferred.

The granulation can also, for example, be carried out by a - preferably heatable - High-Shear-Mixer (e.g. Diosna® P1/6). In this case, the providing step, the melting step and the granulating step can be regarded as one process with different sequences of special parameters. The first sequence can be the providing step without heating, the second sequence can be a mixture of providing step and melting step with heating, sequence three can include parts of melting step and granulating step. Preferred parameters of the sequences can be dependent on the chosen components (a), (b) and optionally (c) and (d).

In a preferred embodiment, the granulation can be carried out with a melt screw extruder (e.g. ThermoFisher® Eurolab 16), wherein the providing step and the granulating step can be unified in one continuous process. Generally, a temperature gradient can be applied, preferably between 70 °C to 200 °C.

In another possible embodiment, the agglomeration step is carried as wet granulation. In this embodiment the mixture of components (a), (b), optionally (c) and optionally (d) is wetted with a granulation liquid or suspended in a granulation liquid. The granulation liquid preferably further comprises a binder. Preferably, the granulation liquid, containing a binder, is a solution or a suspension, preferably a solution. Suitable liquids for preparing the granulation liquid are, for example, water, alcohols and mixtures thereof. A mixture of water and ethanol is preferred.

The providing and the agglomerating step can be carried out in known granulation apparatuses, for example in a Diosna® P1/6. or in a Glatt® GPCG 3.

In a preferred embodiment, the agglomeration conditions in step (1-11) or (2-11) are chosen such that the resulting agglomerated pharmaceutical composition comprises a volume mean particle size (D50) of 5 to 500 μm , more preferably of 20 to 250 μm , further more preferably of 50 to 200 μm .

The bulk density of the agglomerated pharmaceutical composition made by the process of the present invention generally ranges from of 0.1 to 0.85 g/ml, preferably of from 0.25 to 0.85 g/ml, more preferably of from 0.3 to 0.75 g/ml.

In a preferred embodiment the composition has a bulk density of 0.5 to 0.8 g/ml when used for direct compressing and 0.1 to 0.5 when used for dry compaction.

The Hausner factor of the agglomerated (or granulated) composition is less than 1.3, preferably less than 1.2 and most preferably less than 1.15. The agglomerated pharmaceutical composition resulting from step (iii) of the invention preferably possesses Hausner ratios in the range of 1.02 to 1.5, preferably of 1.05 to 1.4, more preferably between 1.08 to 1.3. The Hausner ratio is the ratio of tapped density to bulk density. Bulk density and tapped density are determined according to USP 24, Test 616 "Bulk Density and Tapped Density".

The compression step (1-III) or (2-III), can be carried out on a rotary press, e.g. on a Fette® 102i (Fette GmbH, Germany) or a Riva® piccola (Riva, Argentina). If a rotary press is applied, the main compaction force usually ranges from 1 to 50 kN, preferably

from 2 to 40 kN, more preferably from 3.5 to 30 kN. The resulting tablets usually have a hardness of 30 to 100N, preferably of 50 to 85 N.

5 The shell of the tablets of the second preferred embodiment of the present invention is applied in process step (2-IV). Said step comprises coating the tablet core with a coating comprising preferably components (b) and optionally (c) and/or (d). Preferably, the coating comprises components (b), (c) and a plasticizer.

10 The coating process is generally carried out in a continuously process in a pan coater or a fluid bed dryer. The coating process is preferably carried out on a pan coater, e.g. on a Lodige LHC 25 (Lodige GmbH, Germany). If a pan coater is applied, the spray pressure usually ranges from 0,8 - 2 bar, preferably from 1 - 1.5 bar. The product temperature varies according to the applied polymer. Usually the product temperature is adjusted by 20 - 40 °C, preferably from 32 - 38 °C.

15

The coating usually has a thickness of 0.01 to 2 mm, preferably from 0.1 to 1.5 mm, more preferably from 0.2 to 1 mm.

20

After having received the compressed tablets, in both preferred processes the compressed tablet could be film-coated (step 1-IV or 2-V).

In the present invention, the following three types of film-coatings are possible:

25

- e1) film-coating without effecting the release of the active ingredient (preferred),
- e2) gastric juice resistant film-coatings,
- e3) retard coatings.

30

Film-coatings without effecting the release of the active ingredient are preferred. Generally, said coating can be water-soluble (preferably having a water solubility at 25 °C of more than 250 mg/ml). With gastric juice resistant coatings, the solubility depends on the pH of the surroundings. Retard coatings are usually non-soluble (preferably having a water solubility at 25 °C of less than 10 mg/ml).

Generally, film-coatings e1) were prepared using cellulose derivatives, poly(meth)acrylate, polyvinyl pyrrolidone, polyvinyl acetate phthalate, and/or shellac or natural rubbers such as carrageenan.

- 5 Preferred examples of coatings, which do not effect the release of the active ingredient, include methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyvinyl pyrrolidone (PVP) and mixtures thereof. These polymers generally have a median molecular weight of 10,000 to 150,000 g/mol.

10

A preferred polymer is HPMC, most preferably a HPMC having a median molecular weight of 10,000 to 150,000 g/mol and a median level of substitution of $-OCH_3$ -residues of 1.2 to 2.

- 15 Examples of gastric juice resistant coatings e2) are cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP and polyvinyl acetate phthalate (PVAP). Examples of retard coatings e3) are ethyl cellulose (EC, commercially available e.g. as Surelease®) and poly(meth)acrylate (commercially available e.g. as Eudragit® RL or RS and US).

20

The coating e) can be free of active ingredient. However, it is also possible that the coating contains active ingredient (tasocitinib). In such a case, that amount of active ingredient would function as an initial dose. In such a case the coating e) preferably comprises 1 to 45 wt.%, preferably 5 to 35 wt.%, most preferably 10 to 30 wt.% of tasocitinib, based on the total amount of tasocitinib contained in the tablet. In this embodiment, the coating preferably is a coating, which does not effect the release of tasocitinib.

25

In case the film coating does not contain tasocitinib (which is preferred), it usually has a thickness of 2 μm to 100 μm , preferably from 20 to 60 μm . In case of a coating containing tasocitinib, the thickness of the coating is usually 10 μm to 2 mm, more preferably from 50 to 500 μm .

30

Accordingly, in a further embodiment the subject invention relates to a tablet in which 1 to 45 wt.%, preferably 5 to 35 wt.%, most preferably 10 to 30 wt.% of the total amount

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of the tasocitinib contained in the tablet, are present as initial doses having immediate release, and 55 to 99 wt.%, preferably 65 to 95 wt.%, most preferably 70 to 90 wt.% of the active ingredient are present in the tablet as a modified release formulation.

- 5 The third preferred embodiment of the present invention relates to a multiple unit pellet system (MUPS). As the name implies, this type of dosage form comprises more than one discrete unit. Typically, such systems comprise 2 to 50, preferably 3 to 30 discrete units. Typically, such discrete units are coated spheroids. Preferably, such coated spheroids are filled into capsules, preferably hard gelatin capsules. Alternatively, such
10 coated spheroids are compressed into tablets.

Hence, a further subject of the present invention is a process for manufacturing an oral modified release dosage form comprising tasocitinib, comprising the steps of

- 15 (3-I) providing a pellet core,
(3-II) spraying a solution or suspension comprising component (a) and optionally (d) onto the pellet core,
(3-III) spraying a solution or suspension comprising component (b) and optionally (c) and/or (d) onto the pellet, preferably onto the pellet
20 resulting from step (3-II),
(3-IV) optionally blending the pellets with components (b) and (c) and/or (d);
and
(3-V) further processing the resulting mixture into a final oral dosage form.

- 25 In this pellet layering embodiment, the present invention provides a process for the manufacture of a modified release dosage form comprising tasocitinib, employing a pellet layering process.

- In step (3-I) a pellet core is provided. Preferably, the pellet core is a so-called neutral
30 pellet core, that means it does not comprise an active ingredient. Such pellet cores are known in the art as non-pareils. The pellet core can be made of suitable materials, e.g. cellulose, sucrose, starch or mannitol or combinations thereof.

- Suitable pellet cores are commercially available under the trade name Cellets* and
35 preferably comprise a mixture of lactose and microcrystalline cellulose.

Furthermore, in a preferred embodiment, pellet cores commercially available as Suglets® are used. Those preferred pellet cores comprise a mixture of corn starch and sucrose. The mixture usually comprises 1 to 20 wt.% corn starch and 80 to 99 wt.% sucrose, in particular, about 8 wt.% corn starch and 92 % sucrose.

- 5 In step (3-II) the tasocitinib is dissolved or suspended in a solvent. The solvent can be water, a pharmaceutically acceptable organic solvent or mixtures thereof. Preferably, the solvent is water or an alcohol. Most preferably, the solvent is methanol.

- 10 The solution or dispersion of tasocitinib can comprise further excipients (d). It preferably comprises a solubilizer (d1) and/or a plasticizer (d8). Generally, it is noted that all comments made above regarding the excipients (d) used in the present invention also apply for the processes of the present invention. In addition, the solution or dispersion may comprise anti-sticking agents and lubricants.

- 15 The resulting emulsion or suspension is sprayed onto the pellet core, preferably by a fluid bed dryer, e.g. Glatt GPCG 3 (Glatt GmbH, Germany).

- 20 Subsequently, the spraying step is repeated. In step (3-III) a solution or suspension comprising component (b) and optionally (c) and/or (d) is sprayed onto the pellet resulting from step (3-II). In the spraying step (3-III), preferably solubilizer (d1) and/or plasticizer (d8) are used as excipients.

- 25 Alternatively, the spraying steps (3-II) and (3-III) can be combined. In such a case, the solution or dispersion of tasocitinib further comprises components (b) and optionally (c) and/or excipients (d).

- 30 In a preferred embodiment, the spraying conditions are chosen such that the resulting coated spheroids have a mean particle size (D50) of 10 to 1000 μm , more preferably of 50 to 800 μm , further more preferably of 100 to 750 μm , most preferably of 250 to 650 μm .

The coated spheroids of the present invention (i.e. the primary pharmaceutical composition) may be used to prepare suitable solid oral dosage forms with modified released properties. That means, the primary pharmaceutical composition can be

further processed to give a "final pharmaceutical composition", i.e. to give a final oral dosage form.

Hence, the present invention encompasses a process for producing oral dosage forms comprising a pharmaceutical composition as received by the above-described pellet layering process, comprising the steps of

(3-V-i) optionally mixing the granulates as received by the above-described pellet layering process with further excipients,

10 (3-V-ii) further processing the resulting mixture into a final oral dosage form.

Preferably, step (ii) comprises

15 (3-V-ii-a) filling the resulting mixture into capsules,

(3-V-ii-β) filling the resulting mixture into sachets, or

(3-V-ii-γ) compressing the resulting mixture into tablets. The tablets can be film-coated (e), as described above.

20 Generally, it is noted that all comments made above with respect to the tablets of the present invention also apply for the process of manufacturing such a tablet and the use of the tablet of the present invention.

25 Consequently, further subjects of the present invention are tablets obtainable by any of the processes as described above.

All explanations above given for the process of the present invention also apply for the tablet of the present invention.

30 The release profile of a non-coated tablet or a coated tablet, wherein the coating is free of drug, usually shows a constant release as determined by method USP (paddle). Preferably, the slope of the initial drug release is less than 0.6 to 0.8 % per minute.

35 In a further aspect the present invention is related to an osmotic controlled release device comprising tofacitinib, preferably in form of a tablet.

The controlled release device comprises:

- (A) a core comprising tofacitinib and an osmotic agent, and
- (B) a water-permeable coating comprising a non-erodible polymer.

5

It is noted that all explanations made above for preferred embodiments (e.g. preferred tofacitinib salts, preferred non-erodible polymers, preferred excipients, preferred ratios and amounts) apply as well for the below described second aspect.

- 10 In a preferred embodiment of the osmotic controlled release devices the water-permeable, non-dissolving coating, which comprises the non-erodible material surrounding the core, controls the influx of water to the core from an aqueous environment, so as to cause drug release by extrusion of some or all of the core to the environment of use.

15

The osmotic agent contained in the core of this device may be an aqueous-swella-
ble hydrophilic polymer or it may be an osmogen. The coating is preferably polymeric,
aqueous-permeable and has at least one delivery port. Examples of such devices are
disclosed more fully in U.S. Patent No. 6,706,283, the disclosure of which is hereby
20 incorporated by reference.

- Preferably, the osmotic agent creates a driving force for the transport of water from the
environment of use into the core of the device. Exemplary osmotic agents are water-
swella-
ble hydrophilic polymers. The amount of water-swella-
ble hydrophilic polymers
25 present in the core may range from about 5 to about 80 wt.%, preferably 10 to 50 wt.%,
based on the total weight of the core. Exemplary materials include hydrophilic vinyl and
acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO),
polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl
methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP) and
30 cross-linked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers and PVA/PVP
copolymers with hydrophobic monomers such as methyl methacrylate, vinyl acetate,
and the like, hydrophilic polyurethanes containing large PEO blocks, sodium
croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose
(HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and
35 carboxyethyl cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum

and sodium starch glycolate. Typical classes of suitable osmotic agents are water-soluble organic acids, salts and sugars that are capable of imbibing water, to thereby effect an osmotic pressure gradient across the barrier of the surrounding coating. Typical useful osmogens include magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate, mannitol, xylitol, urea, sorbitol, sucrose, glucose, fructose, lactose, and mixtures thereof. The core may include a wide variety of additives and excipients that enhance the performance of the dosage form or that promote stability, tableting or processing.

Such osmotic delivery devices may be fabricated in various geometries including bilayer, wherein the core comprises a drug layer and a sweller layer adjacent to each other; including trilayer, wherein the core comprises a sweller layer "sandwiched" between two drug layers; and including concentric, wherein the core comprises a central sweller composition surrounded by the drug layer.

The coating of the device comprises a non-erodible coating (B), which preferably is insoluble in water but permeable to water and substantially impermeable to drug and excipients contained therein. The coating preferably contains one or more exit passageways or ports in communication with the drug-containing layer(s) for delivering the drug composition. Preferably, the drug-containing layer(s) of the core contains the drug composition, while the sweller layer consists of an expandable hydrogel, with or without additional osmotic agents. When placed in an aqueous medium, the device imbibes water through the membrane, causing the composition to form a dispensable aqueous composition and causing the hydrogel layer to expand and push against the drug-containing composition, forcing the composition out of the exit passageway. The composition can swell, aiding by forcing the drug out of the passageway. A drug can be delivered from this type of delivery system either dissolved or dispersed in the composition that is expelled from the exit passageway.

In the case of a bilayer geometry, the delivery port(s) or exit passageway(s) may be located on the side of the tablet containing the drug composition or may be located on both sides of the tablet or even on the edge of the tablet so as to connect both the drug layer and the sweller layer with the exterior of the device. The exit passageway(s) may be produced by mechanical means or by laser drilling or by creating a difficult-to-coat

region on the tablet by use of special tooling during tablet compression or by other means.

5 A particularly useful embodiment of an osmotic device comprises: (A) a single-layer compressed core comprising: (i) tofacitinib (ii) a modified cellulose, in particular hydroxyethylcellulose, and (iii) an osmotic agent, wherein the modified cellulose is present in the core from about 2.0% to about 35% by weight and the osmotic agent is present from about 15% to about 70% by weight; (B) a water-permeable layer surrounding the core; and at least one passageway within the layer for delivering the
10 drug to a fluid environment surrounding the tablet.

Several disintegrants tend to form gels as they swell with water, thus hindering the drug delivery from the device. Non-gelling, non-swelling disintegrants provide a more rapid dispersion of the drug particles within the core as water enters the core. Preferred
15 non-gelling, non-swelling disintegrants are resins, preferably ion-exchange resins. A preferred resin is Amberlite™ IRP 88 (available from Rohm and Haas, Philadelphia, PA). When used, the disintegrant is present in amounts ranging from about 1% - 25% of the core composition.

20 Another example for an osmotic device is an osmotic capsule. The capsule shell or portion of the capsule shell can be semi-permeable.

Coating is conducted in conventional fashion, typically by dissolving or suspending the coating material in a solvent and then coating by dipping, spray coating or preferably
25 by pan-coating. A preferred coating solution contains 5 to 15 wt.% polymer. Typical solvents, useful with the cellulosic polymers mentioned above, include acetone, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane,
30 nitropropane, tetrachloroethane, 1,4-dioxane, tetrahydrofuran, diglyme, water, and mixtures thereof. Pore-formers and non-solvents (such as water, glycerol and ethanol) or plasticizers (such as diethyl phthalate) may also be added in any amount as long as the polymer remains soluble at the spray temperature. Pore-formers and their use in fabricating coatings are described in U.S. Patent No. 5,612,059, the pertinent
35 disclosures of which are incorporated herein by reference.

Coatings may also be hydrophobic microporous layers, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Patent No. 5,798,119, the pertinent disclosures of which are incorporated herein by reference. Such hydrophobic but

5 water-vapor permeable coatings are typically composed of hydrophobic polymers such as polyalkenes, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes and synthetic waxes. Especially preferred hydrophobic microporous coating materials include polystyrene, polysulfones, polyethersulfones, polyethylene,

10 polypropylene, polyvinyl chloride, polyvinylidene fluoride and polytetrafluoroethylene. Such hydrophobic coatings can be made by known phase inversion methods, using any of vapor-quench, liquid quench, thermal processes, leaching soluble material from the coating or by sintering coating particles. In thermal processes, a solution of polymer in a latent solvent is brought to liquid-liquid phase separation in a cooling step. When

15 evaporation of the solvent is not prevented, the resulting membrane will typically be porous. Such coating processes may be conducted by the processes disclosed in U.S. Patent Nos. 4,247,498, 4,490,431 and 4,744,906, the disclosures of which are also incorporated herein by reference.

20 In a preferred embodiment, the oral dosage form of the present invention is suitable for administration once or twice per day, most preferably once per day. Alternatively, the oral dosage form of the present invention can be administered every second day, thrice a week, twice a week or once a week.

25 The present invention also provides the use of the modified release tablet of the present invention as an immunosuppressive agent for organ transplants, xeno transplantation, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease,

30 leukemia. The pharmaceutical composition or the oral dosage form of the present invention can be used as an immunosuppressive agent in a method for organ transplants or xenotransplantation, or for treating lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, Type I diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease,

35 Alzheimer's disease, leukemia, said method comprising administering an effective

amount of the pharmaceutical composition or the oral dosage form in a subject in need thereof.

The present invention is illustrated by the following examples.

5

EXAMPLES

The following commercially available compounds were used in the Examples below:

- | | | |
|----|-----------------------------|---|
| 10 | Eudragit® L100-55 (Rohm): | anionic copolymer of methacrylic acid and acrylic acid ethylester |
| | Eudragit® RL PO (Rohm): | copolymer of acrylic and methacrylic acid esters containing quaternary ammonium groups |
| 15 | Eudragit® RS PO (Rohm): | copolymer of ethyl acrylate, methyl methacrylate and a low content of methacrylic acid ester with quaternary ammonium groups |
| | Kollicoat® MAE 100P (BASF): | methacrylic acid copolymer |
| | Kollidon® SR (BASF): | mixture of 80 % hydrophobic polyvinyl acetate, 19 % hydrophilic polyvinyl pyrrolidone, 0.8 % sodium lauryl sulfate and 0.2 % colloidal silicate |
| 20 | Aerosir® 200 (Degussa): | highly dispersed silicium dioxide |
| | Avicel® PH102 (FMC): | microcrystalline cellulose, with D50 particle size of about 100 µm |
| | Lubritab® | hydrogenated vegetable oil |
| 25 | Opadry® | film-coating |
| | Retalac® (Meggle) | spray agglomerated blend of 50 parts lactosemonohydrate and 50 parts hypromellose |

Examples 1 - 3: Formulations Containing a Pore-Forming Material with pH Dependent Solubility

Example 1: Matrix tablet, direct compression

5

Tablet formulation 1:

	Tasocitinib citrate	10 mg (based on the free base)
	Eudragit® L100-55	40 mg
10	Lactose monohydrate	30 mg
	Dicalcium phosphate anhydrate	30 mg
	Aerosil® 200	1 mg
	Magnesium stearate	1 mg
15	All ingredients except magnesium stearate were blended in a free fall mixer for 15 min. Then, sieved (500 µm) magnesium stearate was added and the mixture was blended for further 5 min. The final blend was compressed into tablets.	

Example 2: Matrix tablet, wet granulation

20 Tablet formulation 2:

	Tasocitinib citrate	10 mg (based on the free base)
	Kollicoat® MAE 100P	45 mg
	Lactose monohydrate	25 mg
25	Avicel® PH102	17 mg
	Aerosil® 200	2 mg
	Magnesium stearate	1 mg

30 Tasocitinib, Kollicoat® and lactose were sieved (1.25 mm mesh) into the pot of a Diosna® P1-6 wet granulator and blended for 2 min. This pre-mixture was granulated, adding a suitable amount of water to gain a mixture having a "snow ball" consistency. The wet granulate was sieved (2 mm mesh) and dried for 2 h at 40 °C in a cabinet drier. The dried granulate was sieved (1.25 mm mesh) and Avicel® and Aerosil® (both sieved with 1.25 mm mesh) were added and the resulting mixture was blended for

35 further 15 min in a free fall mixer. Sieved (500 µm mesh) magnesium stearate was

added and the resulting mixture was blended in a free fall mixer for 5 min. The final blend was compressed into tablets.

Example 3: Dry granulation

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Tablet formulation 3:

	Tasocitinib	10 mg (based on the free base)
	Eudragit L 100-55	40 mg
10	GalenIQ 800	30 mg
	Dicalciumphosphat anhydrate	30 mg
	Aerosil® 200	1 mg
	Magnesium stearate	1 mg

- 15 All ingredients, except Aerosil 200 and magnesium stearate, were sieved (1mm mesh) and blended in a free fall mixer for 15 min. The premixture was compacted and the resulting slug was sieved (1mm mesh). Subsequently, Aerosil 200 was added over a sieve (2mm mesh) and blended for further 10 minutes. Then, sieved (500 μm) magnesium stearate was added and the mixture was blended for further 5 min. The
- 20 final blend was compressed into tablets.

Examples 4 - 5: Formulations Containing a Pore-Forming Material with pH Independent Solubility

25 Example 4: Direct compression

Tablet formulation 4:

	Tasocitinib hemi citrate	10 mg (based on the free base)
30	Kollidon® SR	40 mg
	Lactose monohydrate	30 mg
	Dicalcium phosphate anhydrate	30 mg
	Aerosil® 200	1 mg
	Magnesium stearate	1 mg

35

All ingredients, except magnesium stearate, were sieved (1mm mesh) and blended in a free fall mixer for 15 min. Then, sieved (500 μm) magnesium stearate was added and the mixture blended for further 5 min. The final blend was compressed into tablets.

5 Example 5: Wet granulation

Tablet formulation 5:

	Tasocitinib citrate	10 mg (based on the free base)
10	Eudragit® RL PO	45 mg
	Lactose monohydrate	25 mg
	Avicel® PH102	17 mg
	Aerosil® 200	2 mg
	Magnesium stearate	1 mg

15

Tasocitinib, Eudragit® and lactose were sieved (1.25 mm mesh) into the pot of a Diosna® P1-6 wet granulator and blended for 2 min. This pre-mixture was granulated, adding a suitable amount of water to gain a mixture having a "snow ball" consistency. The wet granulate was sieved (2 mm mesh) and dried for 2 h at 40 °C in a cabinet

20 drier. The dried granulate was sieved (1.25 mm mesh) and Avicel® and Aerosil® (both sieved with 1.25 mm mesh) were added and the resulting mixture was blended for further 15 min in a free fall mixer. Sieved (500 μm mesh) magnesium stearate was added and the resulting mixture was blended in a free fall mixer for 5 min. The final blend was compressed into tablets.

25

Example 6: Coated tablet

Tablet formulation 6:

30	Tablet core	
	Tasocitinib	10 mg (based on the free base)
	StarLac®	80 mg
	Dicalciumphosphat anhydrate	10 mg
	Aerosil 200	1 mg
35	Magnesiumstearate	1 mg

All excipients, excluding magnesium stearate, were sieved (800 μ m) and mixed together for 15 min in a free fall mixer. Sieved (500 μ m mesh) magnesium stearate was added and the resulting mixture was blended in a free fall mixer for 5 min. The final blend was compressed into tablets.

5

Tablet coating

	Ethylcellulose	20 mg
	PEG 6000	1 mg
10	TEC	5 mg

The coating process was carried out on a pan coater, e.g. on a Lodige LHC 25 (Lodige GmbH, Germany). The spray pressure usually ranges from 1 - 1.5 bar. The product temperature varies according to the applied polymer from 32 - 38 °C.

15

Example 7: MUPS

Tablet formulation 7:

20	Tasocitinib, micronized	10 mg
	Polyoxyethylenepropylene copolymer	4 mg
	Ethylcellulose:	15 mg
	PEG 4000	4 mg
	Nonpareils	40 mg
25	MCC	200 mg
	Polyvinylpyrrolidone	10 mg
	Lubritab	5 mg
	Aerosil	2 mg
	Opadry	2.5 mg

30

Procedure:

Tasocitinib was suspended together with ethyl cellulose in an aqueous solution of polyoxyethylene propylene copolymer and PEG. The placebo pellets were pre-heated

to 38 °C in a fluid bed dryer. Subsequently the pellets were coated with the suspension, using the following parameter:

	Inlet temperature:	40-80X
5	Product temperature :	35÷40°C
	Spray nozzle:	1 - 2 mm
	Spray pressure:	1 - 2 bar

After sintering at elevated temperature the pellets were blended with MCC and Aerosil® and polyvinylpyrrolidone for 25 min in a tumble blender. Afterwards, Lubritab* was added and the blend was mixed for additional 3 minutes.

The final blend was compressed on a Fette® 102 rotary press, characterized by following parameters:

15

Hardness:	80 - 110 N
Friability:	less than 1 %.

The tablets were film-coated in order to achieve a better compliance with an aqueous solution of Opadry (Colorcon®):

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	Product temperature:	37 - 40°C
	Supply air temperature :	40 - 80°C
	Nozzle diameter:	1,2 mm
25	Spray pressure:	1 -3 bar

Afterwards, the tablets were sintered at 60 °C for 0.5 hour.

Example 8:

30

Tasocitinib citrate	10.0 g (based on free base)
Eudragit® RS PO	84.0 g

API and Eudragit were sieved over a 1000 µm sieve and blended for 15 minutes in a Turbula blender. The resulting blend was extruded in a ThermoFisher extruder. 11.78 g

35

of the resulting extrudate was milled in a Comil, sieved over 800 µm and blended together with 3.5 g RetaLac®, 1.2 g Tablettose 80, 0.1 g Aerosil and 0.2 g magnesium stearate. The resulting blend was compressed to tablets on a Korsch tablet press, each tablet containing 10 mg tasocitinib (based on free base).

5

Example 9:

	Tasocitinib citrate	1.0 g (based on free base)
	Eudragit® RS PO	8.4 g
10	Granulac® 200	3.0 g
	Aerosil 200	0.2 g
	Magnesiumstearate	0.2 g

API, Eudragit and Granulac 200 were sieved over a 1000 µm sieve, blended,
 15 granulated with water/ 2-propanol (1:1) and dried at 40°C. The resulting granulate was sieved over 1000 µm sieve, blended with Aerosil and magnesiumstearate. The resulting mixture was compressed to tablets on a Korsch press, each tablet containing 10.0 mg of tasocitinib (based on free base).

20 Example 10: Osmotic-controlled tabletTablet core:

	Tasocitinib citrate	10 mg (based on the free base)
25	PolyOx® WSR-N80 (Dow)	193 mg
	Xylitol (trade name XYLITAB® 200)	93 mg
	Magnesiumstearate	2 x 2 mg

PolyOx and xylitol are combined and blended in a free fall mixer. The blended material
 30 is passed through a sieve (800 µm). The resulting material is added to a blender, the tasocitinib citrate is added and the resulting mixture is mixed for 15 minutes. Magnesiumstearate (2 mg) is added and the resulting blend is mixed for another 5 minutes. The blend is roller-compacted. The resulting granules are transferred to a free fall mixer. Magnesiumstearate (2 mg) is added and the final blend is mixed for another
 35 15 minutes.

	PEO WSR Coagulant (Dow)	129 mg
	Avicel® PH 200 (FMC)	51.6 mg
	Sodium chloride	17.2 mg
	FD&C #2 Blue Lake	0.6 mg
5	Magnesiumstearate	1 mg

Coagulant, Avicel, sodium chloride and FD&C are mixed in a free fall mixer for 15 minutes. Magnesiumstearate is added and the final blend for the swellable layer is mixed for 15 minutes.

10

Tablet cores are formed by compressing 600 mg (400 mg tofacitinib-containing layer; 200 mg swellable layer, using a rotary tri-layer press (e.g. Elizabeth-HATA AP-55). Feed hopper #1 is filled with the tofacitinib-containing layer, feed hopper #2 is empty and feed hopper #3 is filled with the swellable layer. A tamp force of 50 - 65 kg is used for the tofacitinib-containing layer and the tamp force of 500 - 600 kg is used after hopper #3 and the final compression force is approximately 14 kN, resulting in tablets of approximately 15 kP hardness.

15

Coating

20

	Polyethylene glycol	8.0 mg
	Water	40 mg
	Acetone	920 mg
	Cellulose acetate	32 mg

25

Polyethylene glycol (PEG 3350) is dissolved in water and acetone is added to the solution. The cellulose acetate (CA 398-10 from Eastman Fine Chemical) is added to the solution and the resulting solution is mixed until homogeneous. The coating solution is applied to the tablet cores by using a pan coater, e.g. on a Lodige LHC 25 (Lodige GmbH, Germany). The spray pressure usually ranges from 1 - 1.5 bar. The product temperature varies according to the applied polymer from 32 °C - 38 °C. The so-coated tablets are dried in a convection oven. One 1200 µm diameter hole is then laser-drilled in the coating on the drug-containing composition side of the tablet to provide one delivery port per tablet.

30

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Claims

1. Oral dosage form for modified release comprising
 - (a) tasocitinib, and
 - (b) a non-erodible material.
2. Oral dosage form according to claim 1, wherein tasocitinib is contained in an amount of 1 to 60 wt.%, based upon the total weight of the oral dosage form.
3. Oral dosage form according to claim 1 or 2, wherein the non-erodible material has a solubility in water at 25 °C at a pH of 5.0 of less than 33 g/l.
4. Oral dosage form according to anyone of the previous claims, wherein the non-erodible material has a solubility in water at 25 °C at a pH of 7.0 of more than 33 g/l.
5. Oral dosage form according to anyone of the previous claims, wherein the non-erodible material is a non-erodible polymer, preferably having a weight average molecular weight from 30,000 to 3,000,000 g/mol.
6. Oral dosage form according to anyone of the previous claims, wherein the non-erodible material is contained in an amount of 5 to 80 wt.%, based upon the total weight of the oral dosage form.
7. Oral dosage form according to any of the previous claims, further comprising a pore-forming material (c).
8. Oral dosage form according to claim 7, wherein the pore-forming material has a solubility in water at 25 °C and at a pH of 5.0 of more than 50 g/l.
9. Oral dosage form according claims 7 or 8, wherein the pore-forming material is contained in an amount of 1 to 50 wt.%, preferably from 5 to 40 wt.%, based upon the total weight of the oral dosage form.
10. Oral dosage form according to anyone of the previous claims, further comprising at least one further excipient (d) selected from solubilizers, fillers,

lubricants, disintegrants, glidants, anti-sticking agents, plasticizers and mixtures thereof.

5 11. Oral dosage form according to anyone of the previous claims in form of a matrix tablet.

10 12. Oral dosage form according to anyone of claims 1 to 10 in form of a tablet comprising a core and a shell, wherein the core comprises components (a) and optionally (c) and/or (d) and wherein the shell comprises components (b) and optionally (c) and/or (d).

13. Oral dosage form according to anyone of claims 1 to 10 in form of a multiple unit pellet system.

15 14. Process for manufacturing a tablet according to anyone of claims 1 to 11 comprising the steps of

(1-1) providing components (a), (b), optionally (c), and optionally (d),
 (1-11) optionally agglomerating the components of step (I) to yield granules,
 (1-111) compressing the mixture resulting from step (I) or (II) into tablets; and
 20 (1-IV) optionally film-coating the tablets.

15. Process for manufacturing a tablet according to anyone of claims 1 to 10 or 12 comprising the steps of

25 (2-I) mixing components (a) and optionally (c) and/or (d),
 (2-II) optionally agglomerating the components of step (I) to yield granules,
 (2-III) compressing the mixture into tablets, and
 (2-IV) coating the tablets with a coating comprising components (b) and optionally (c) ad/or (d).

30 16. Process for manufacturing an oral dosage form according to anyone of claims 1 to 10 or 13 comprising the steps of

(3-I) providing a pellet core,
 (3-II) spraying a solution or suspension comprising component (a) and optionally (d) onto the pellet core,

5

- (3—1) **1** spraying a solution or suspension comprising component (b) and optionally (c) and/or (d) onto the pellet, preferably onto the pellet resulting from step (3-11),
- (3-IV) optionally blending the pellets with components (b) and (c) and/or (d);
- and
- (3-V) further processing the resulting mixture into a final oral dosage form.

INTERNATIONAL SEARCH REPORT

75

International application No
PCT/EP2012/000353

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/515 A61K9/20 A61K9/28 A61K9/22 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal , WPI Data, BIOSIS, EMBASE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	"TASOCITINIB ORAL TABLET COMPOSITION", I.P.COM JOURNAL, I.P.COM INC. , WEST HENRIETTA, NY, US, 4 January 2011 (2011-01-04) , XP013141896, ISSN: 1533-0001 the whole document -----	1-16
X	WO 03/048162 AI (PFIZER PROD INC [US] ; FLANAGAN MARK EDWARD [US] ; LI ZHENG JANE [US]) 12 June 2003 (2003-06-12) cited in the application page 7, lines 9-15 claims -----	1-16
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Herrera, Suzanne

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/000353

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Drug Approval Package

Xeljanz (tofacitinib) Tablets
Company: Pfizer Inc.
Application No.: 203214
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**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
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

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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 tofacitinib 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 $\leq 10\%$ 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 tofacitinib 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 C_{max} (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 ethinylloestradiol 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 α 1-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.

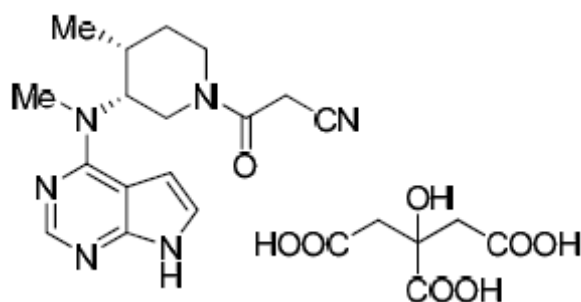


Figure 1: Molecular structure of tofacitinib

Table 2: Tofacitinib physical chemical properties

Molecular Formula	C ₁₆ H ₂₀ N ₆ O•C ₆ H ₈ O 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	<ul style="list-style-type: none"> • 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

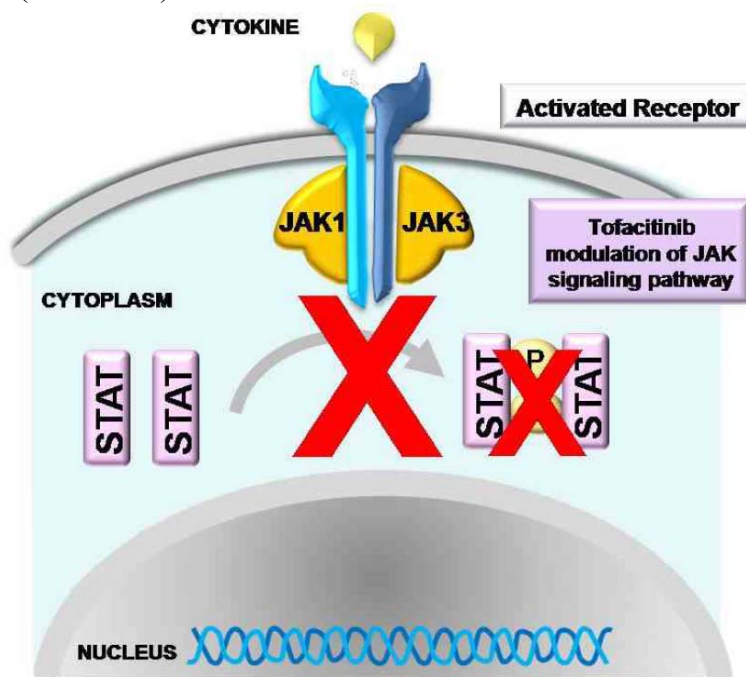
Drug Product

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 γ c-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.

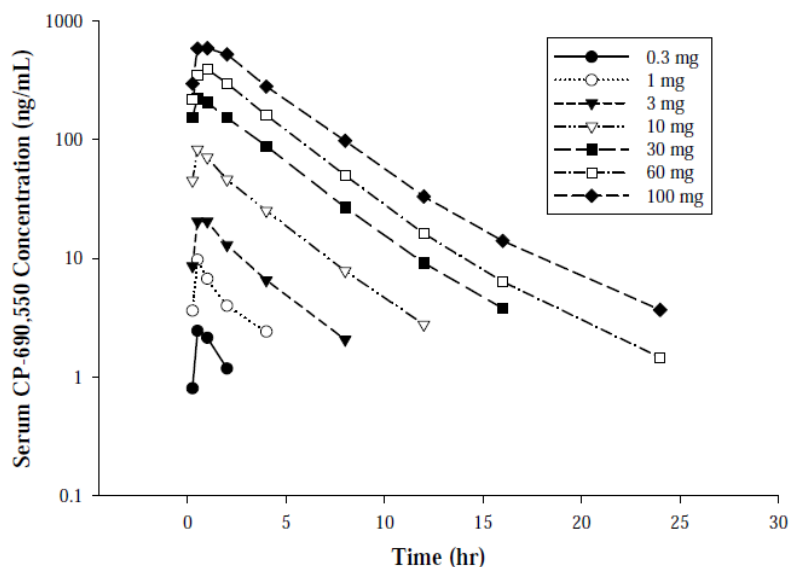


Figure 3: Mean Serum CP-690,550 Concentrations vs Times Following Administration of a Single Oral OPC Dose of CP-690,550 to Fasted Healthy Subjects
(Source – Figure A, Study A3921002 report)

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-Tlast} (ng*hr/mL)	AUC _{0-inf} (ng*hr/mL)	C _{max} (ng/mL)	T _{max} † (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 T_{max}

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.

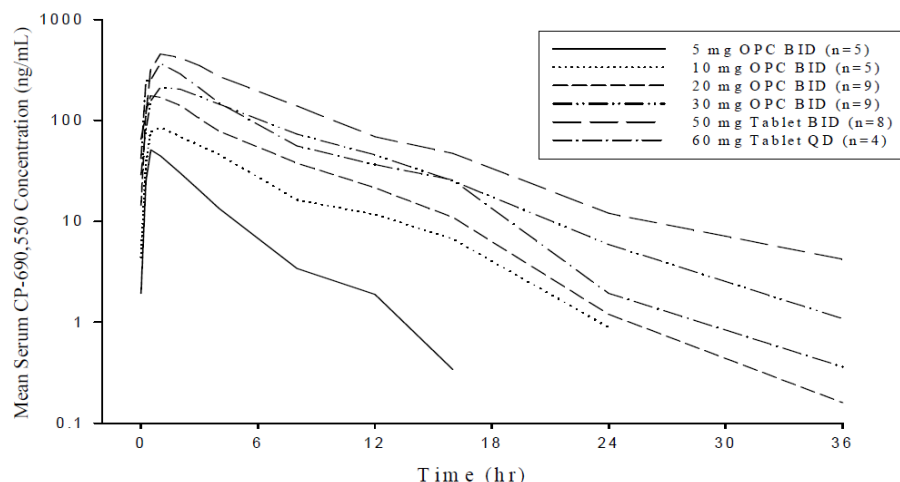


Figure 4: Mean Serum CP-690,550 Concentrations Versus Time on Day 14 Following Multiple Oral Dosing with CP-690,550 in Medically Stable Subjects with Psoriasis
(Source – Figure 1, Study A3921003 report)

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		$AUC_{0-\tau}$ ng h/mL		R_{ac}	T_{max} h ^a		$t_{1/2}$ hr
	Day 1	Day 14	Day 1	Day 14		Day 1	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 t_{max}

^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-alpha¹. 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 C_{max} values from group means in Phase 1 studies (Figure 5) show that majority of AUC and C_{max} 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-∞)	C _{max}	AUC(0-∞)	C _{max}
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 report [Table 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)

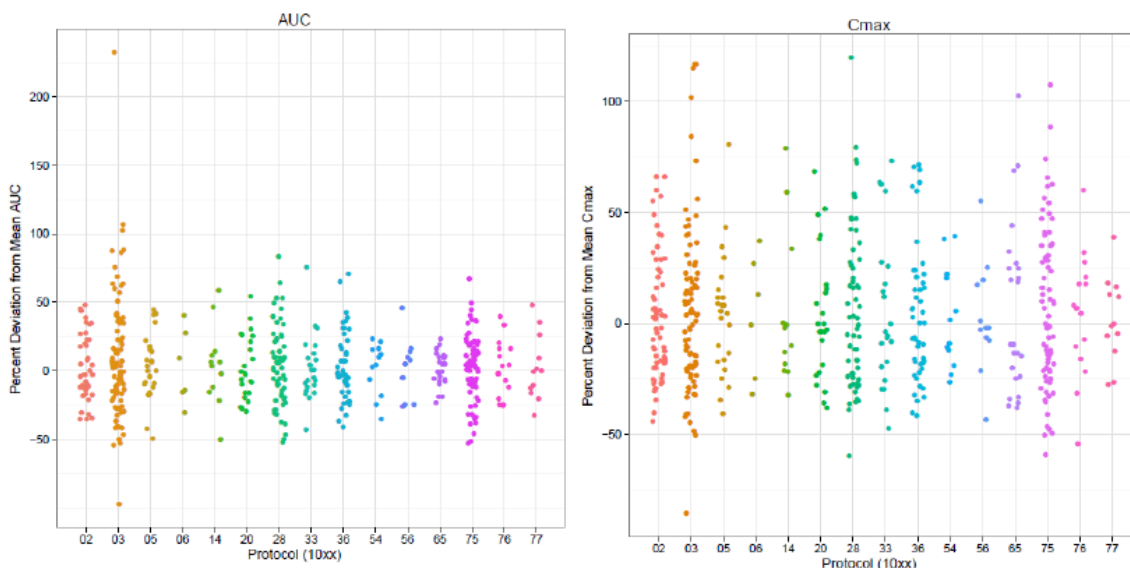


Figure 5: Percent deviation of individual tofacitinib AUC and Cmax values from group means following oral administration in healthy subjects

(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 (f_u) in humans to be 0.61. Tofacitinib was shown to bind moderately to human serum albumin ($f_u = 0.51$) but does not bind to alpha1-acid glycoprotein ($f_u \sim 1$). 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 μ M 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)

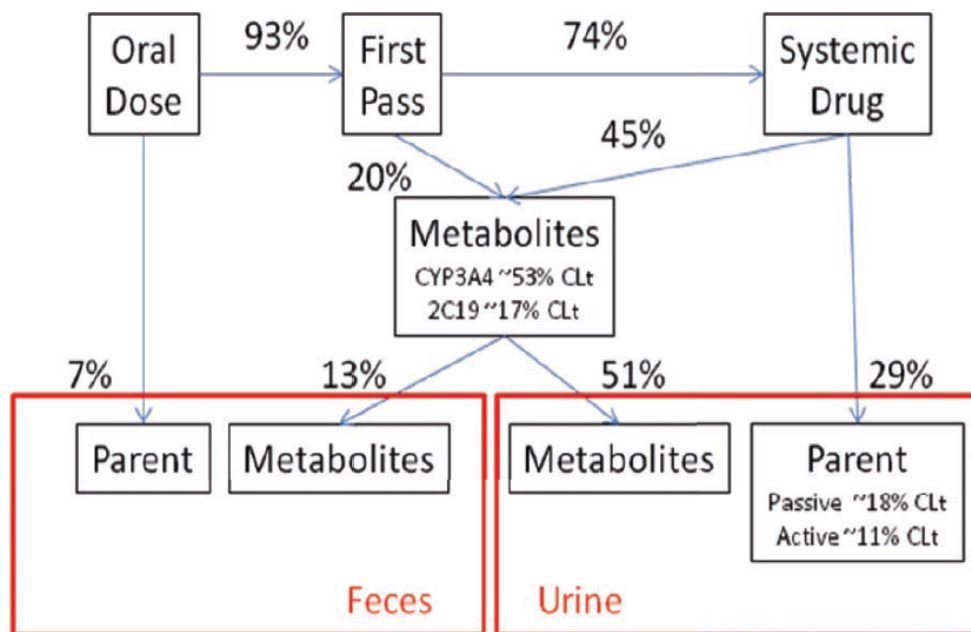


Figure 6: Mass Balance Model for Tofacitinib Following Oral Administration based on Mass Balance and Absolute Bioavailability Study

(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

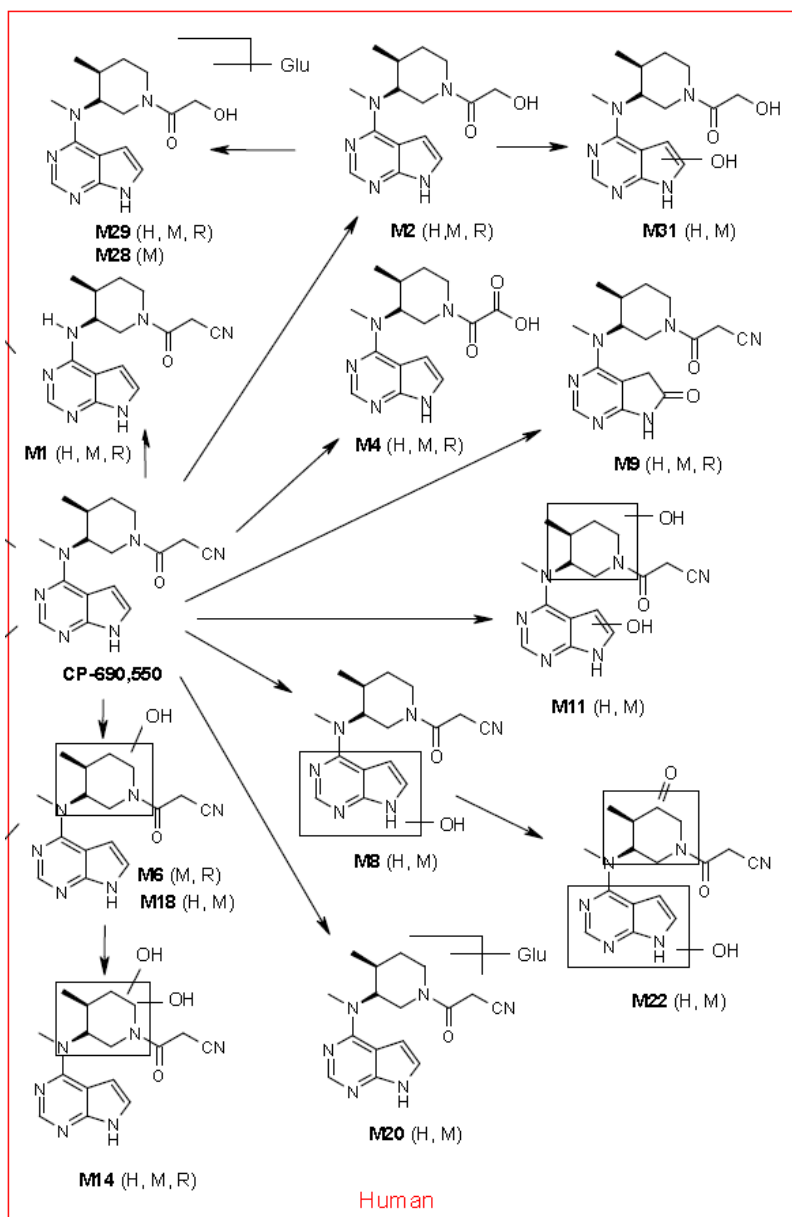
Metabolites	m/z	Ret. Time (min)	Percent of Dose							
			Subject #						Mean	SD
			1	2	3	4	5	6		
M14	345	8.3	3.2	0.7	1.1	4.5	3.3	6.2	3.2	2.1
M4	318	12.4	4.4	5.3	1.4	5.5	2.6	4.5	3.9	1.6
M20, M11, M29	489, 345, 480	15.1	4.8	8.0	4.7	7.5	5.8	6.6	6.2	1.4
M1, M2	299, 304	17.6	0.8	7.3	7.4	7.9	10.4	10.9	7.4	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 $\leq 10\%$ 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 (CL_r) of CP-690,550 were obtained in healthy subjects in Phase 1 studies. The overall mean estimate of CL_r 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 C_{max} 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).

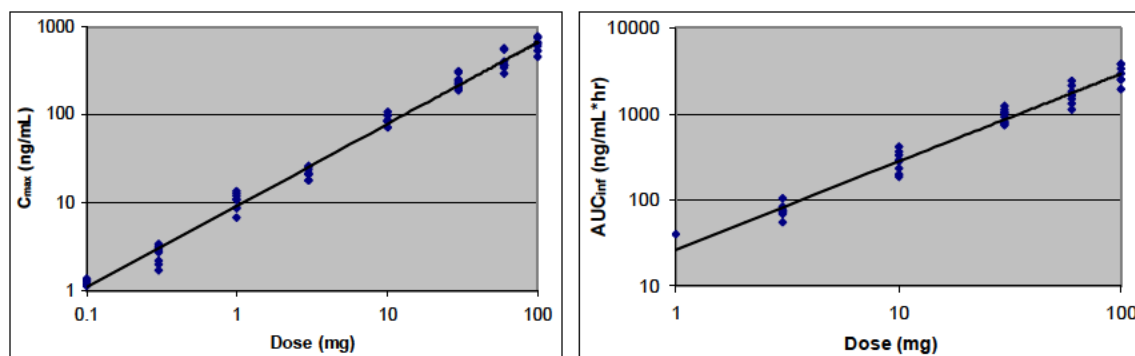


Figure 8: Assessment of dose proportionality for C_{max} and AUC after single-dose (log-scale)

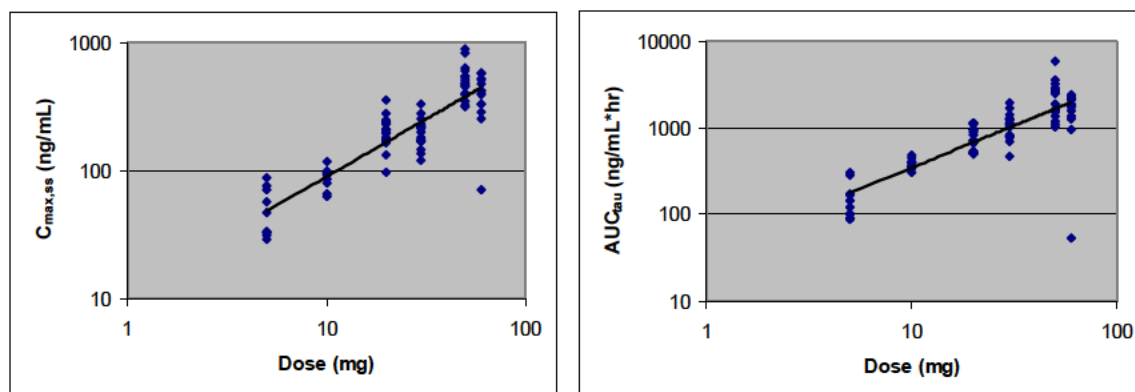


Figure 9: Assessment of dose proportionality for $C_{max,ss}$ and AUC_{tau} after multiple-dose (log-scale)

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

* (PK metrics) = Intercept \cdot (Dose)^{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, C_{max}, C_{min}) 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.

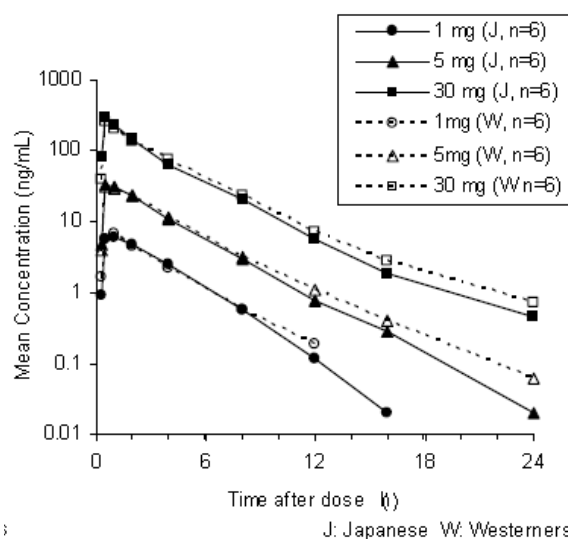


Figure 10: Mean plasma concentration of CP-690,550 following single oral dose administration in healthy Japanese and Western subjects (semi-log scale)

(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	n	n	n	n	n
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_{1/2} (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 _{0-∞} (ng·hr/mL)	273.8 (13)	NA
AUC ₀₋₂₄ (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 _{avg} (ng/mL)	NA	4.688 (38)
t _{1/2} (hr)	3.319 (12)	2.479 (11)
R _{ss}	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_{1/2}.

(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.

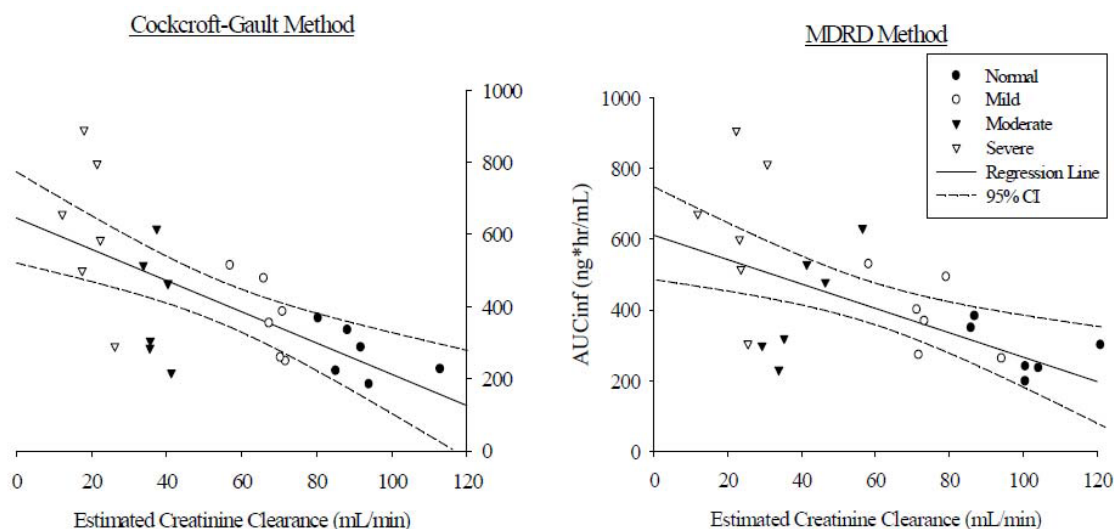


Figure 11: Individual AUC_{0-∞} vs. calculated creatinine clearances following a single 10 mg

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 C_{max}. 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 iothexol 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 iothexol 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
iothexol Serum	0.995	0.911	1.09
Clearance	(0.942, 1.05)	(0.846, 0.982)	(0.997, 1.20)
CrCL	0.948	0.905	1.05
	(0.893, 1.01)	(0.856, 0.956)	(0.967, 1.14)
PAH Renal	0.925	0.946	0.978
Clearance	(0.819, 1.04)	(0.779, 1.15)	(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

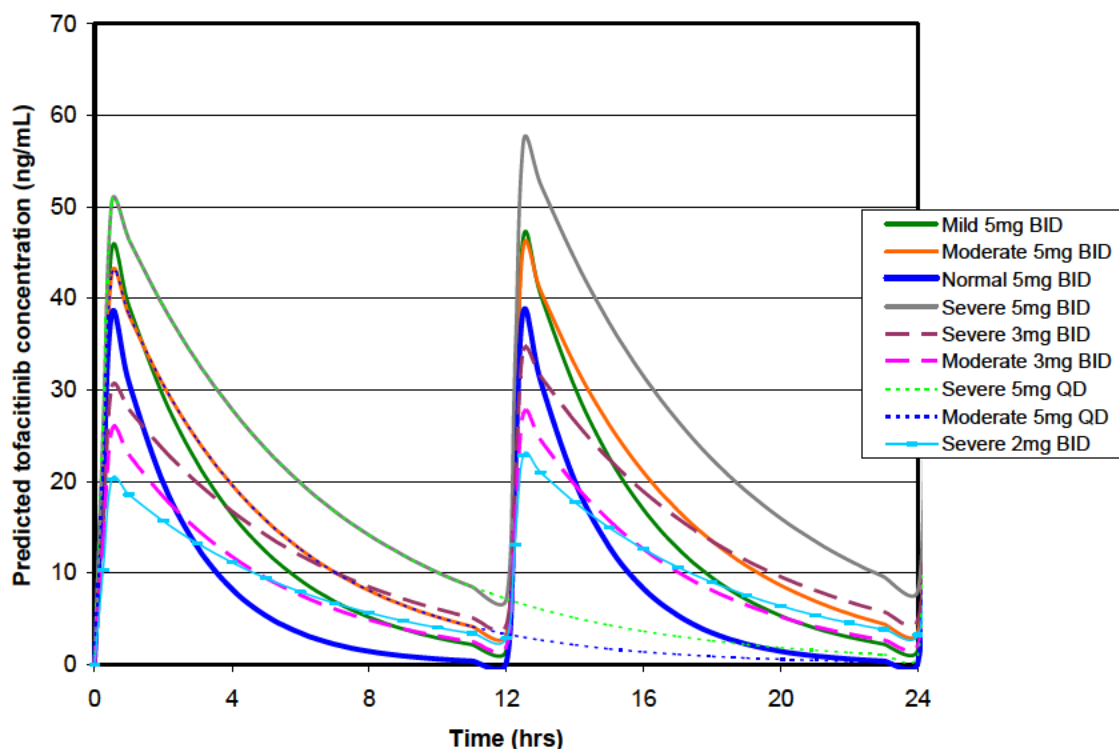


Figure 12: Simulated plasma concentration-time profiles for subjects with normal renal function and renal impairment

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)

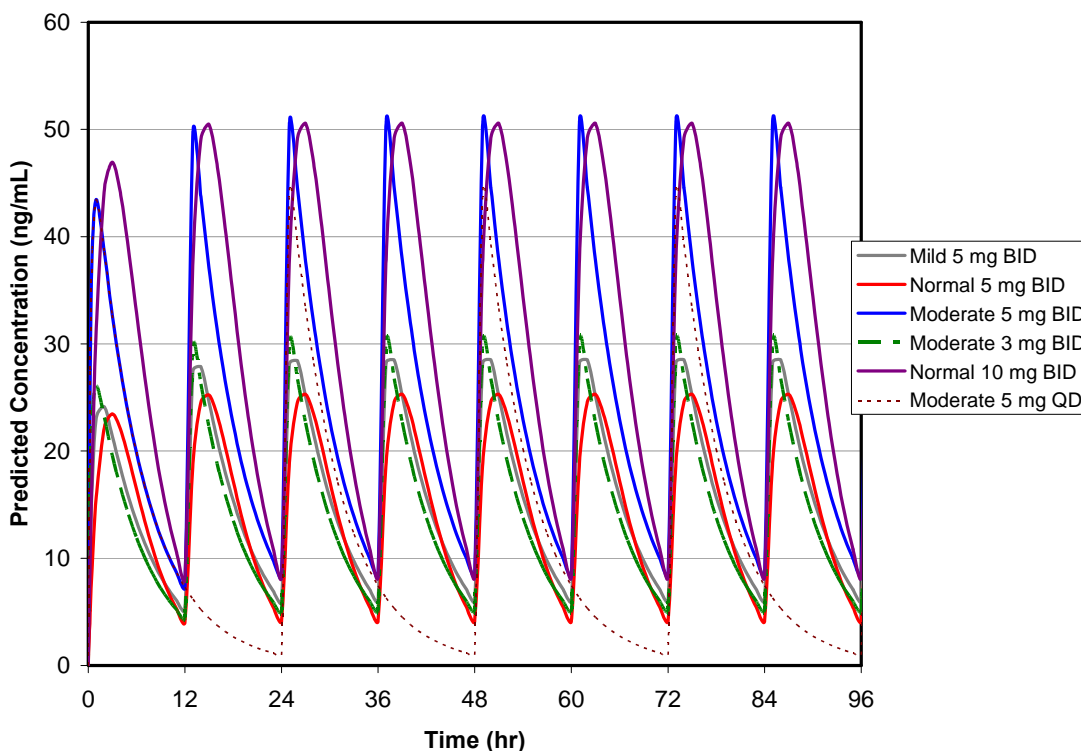


Figure 13: Simulated plasma concentration-time profiles for subjects with normal hepatic function and hepatic impairment

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. IC₅₀ 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 nM² or 0.31 µM for a dose of 10 mg BID, the C_{max}/IC₅₀ 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 µM²), 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	IC ₅₀ µM	[I] / IC ₅₀	[I2] / IC ₅₀
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 = C_{max} 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 IC₅₀ 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 C_{max} 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 monotherapy 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 monotherapy 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 immunosuppressants 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 immunosuppressants 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.

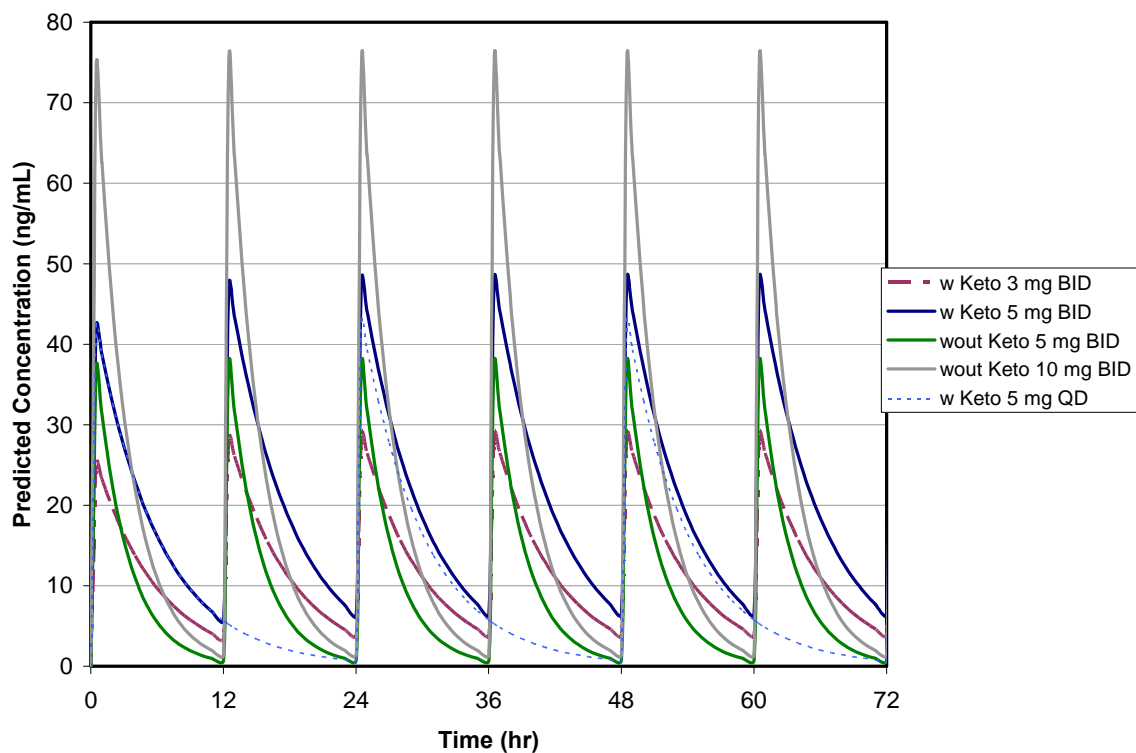


Figure 14: Simulated plasma concentration - time profiles for tofacitinib 3/5/10 mg BID administered with or without ketoconazole
(w: with, wout: without, keto: ketoconazole)

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

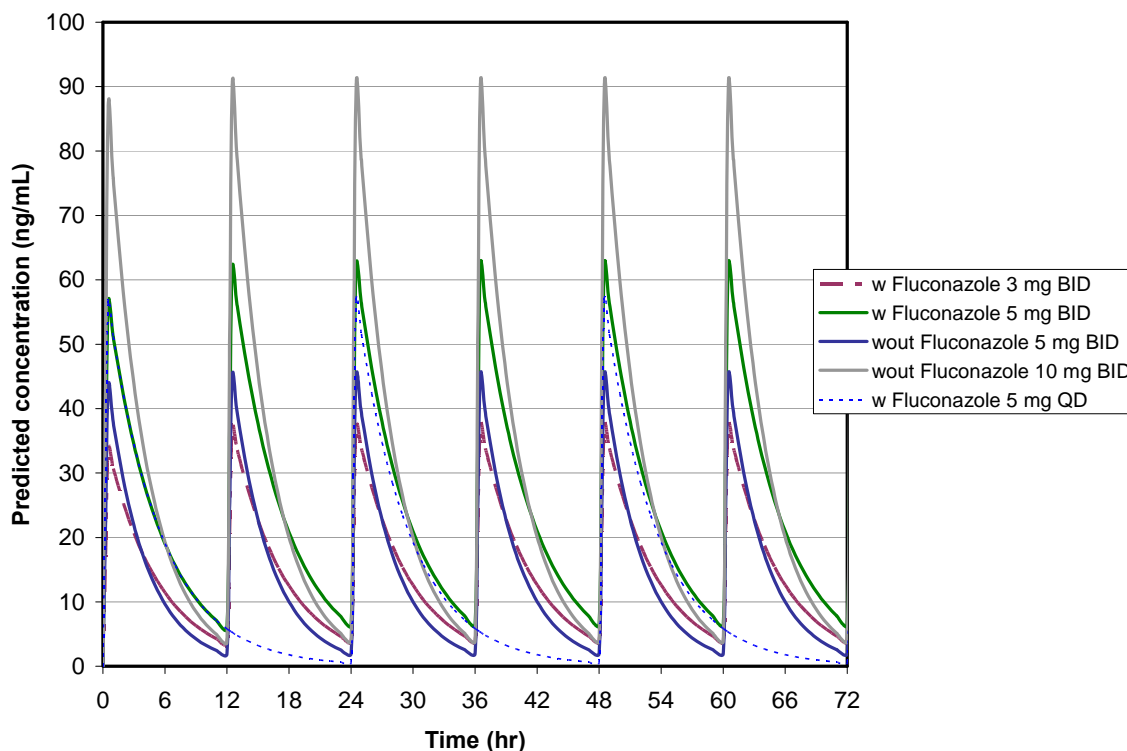


Figure 15: Simulated plasma concentration - time profiles for tofacitinib 3/5/10 mg BID administered with or without fluconazole
(w: with, wout: without)

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 (P_{app}) 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		Ratio	90% CI for Ratio
	Test	Reference	(Test/Reference) of Adjusted Geometric Means ^a	
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} decreased 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		Statistical Comparison	
	Test (Fed)	Reference (Fasted)	Ratio (Test/Ref. %)	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
C _{max} (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
C _{max} (ng/mL)	264.38	356.07	74.25	67.97, 81.11

(Source – Table 21, Section 2.7.1, Summary of Biopharmaceutical 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., [¹³C, ¹⁵N] CP-690,550) was added as an internal standard. The samples were eluted with 13% ammonium hydroxide (NH₄OH) in methanol, evaporated to dryness, and reconstituted with 50% methanol in water. The reconstituted sample was injected into an LC/MS/MS system using a 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., [¹³C, ¹⁵N] CP-690,550) was added as an internal standard. The samples were eluted with 13% NH₄OH in methanol, evaporated to dryness, and reconstituted with 50% methanol in water. The reconstituted sample was injected into an LC/MS/MS system using a Synergi Polar-RP column with a mobile phase of 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	(b) (4)	1.00	≤3.2%	99.1% to 102.1%	1.00 to 100	A3921003 A3921006 A3921013 A3921036
A3929005	Renal Dialysate	(b) (4)	1.00	≤3.3%	99.1% to 100.6%	1.00 to 100	A3921004
A3929006	EDTA Plasma	(b) (4)	1.00	≤5.1%	103.2% to 104.9%	1.00 to 100	A3921004
A3929007	Ultrafiltrate	(b) (4)	1.00	≤3.5%	97.8% to 101.1%	1.00 to 100	A3921004
A3929008	Heparin Plasma	(b) (4)	1.00	≤3.2%	105.0% to 107.5%	1.00 to 100	A3921004 A3921005 A3921006 A3921010 A3921013 A3921014 A3921019 A3921033
A3929011	Heparin Plasma	(b) (4)	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 $1/\text{concentration}^2$ 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 $1/\text{concentration}^2$ 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 [¹³C, ¹⁵N]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 incorporated 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.

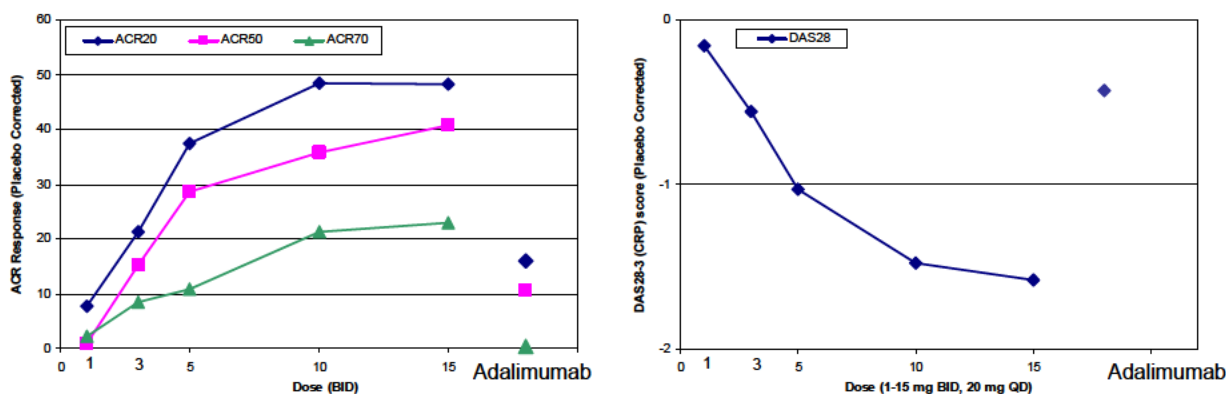


Figure 16: Placebo adjusted change from baseline in ACR 20 ACR 50, ACR 70 at week 12 for study A3921035

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.

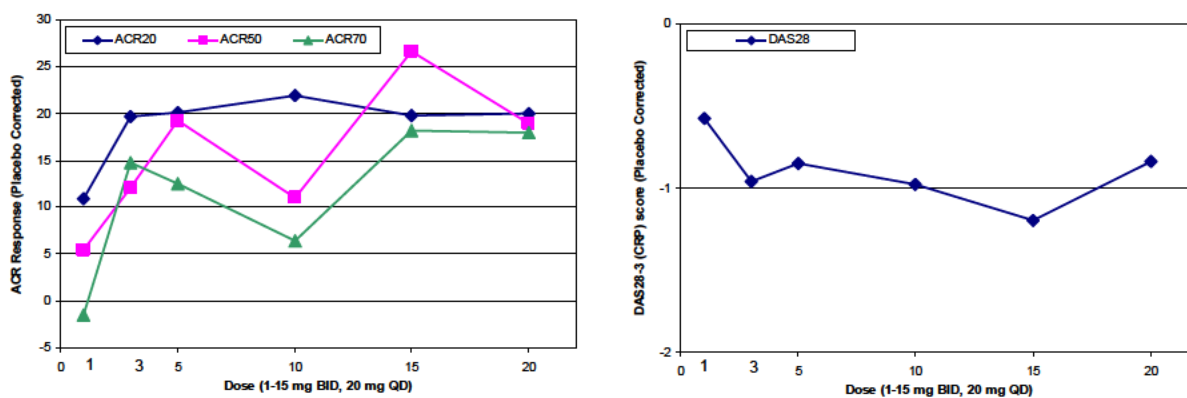


Figure 17: Placebo adjusted change from baseline in ACR 20 ACR 50, ACR 70 at week 12 for study A3921025

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 study 1025 (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.

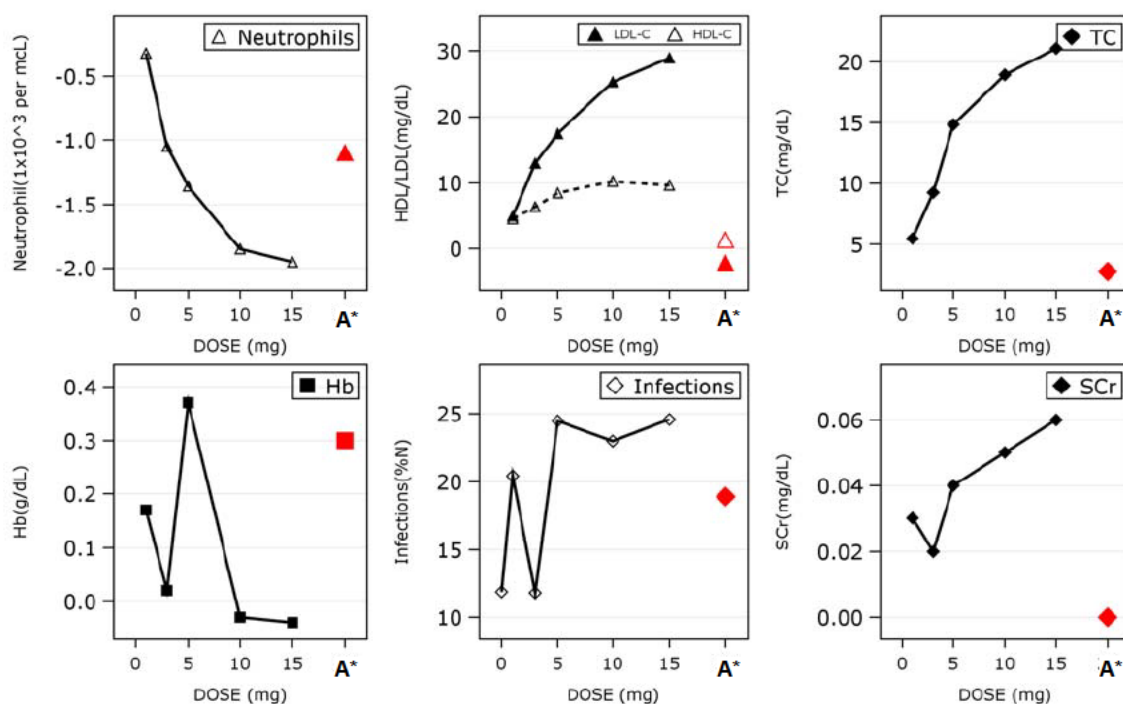


Figure 18: Dose-response relationship for safety endpoints from study 1035. Except infections all other endpoints are shown as placebo adjusted change from baseline to week 12 (delta baseline). Infections are reported as percent incidence at week 12. Active comparator adalimumab is shown as A* on x-axis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

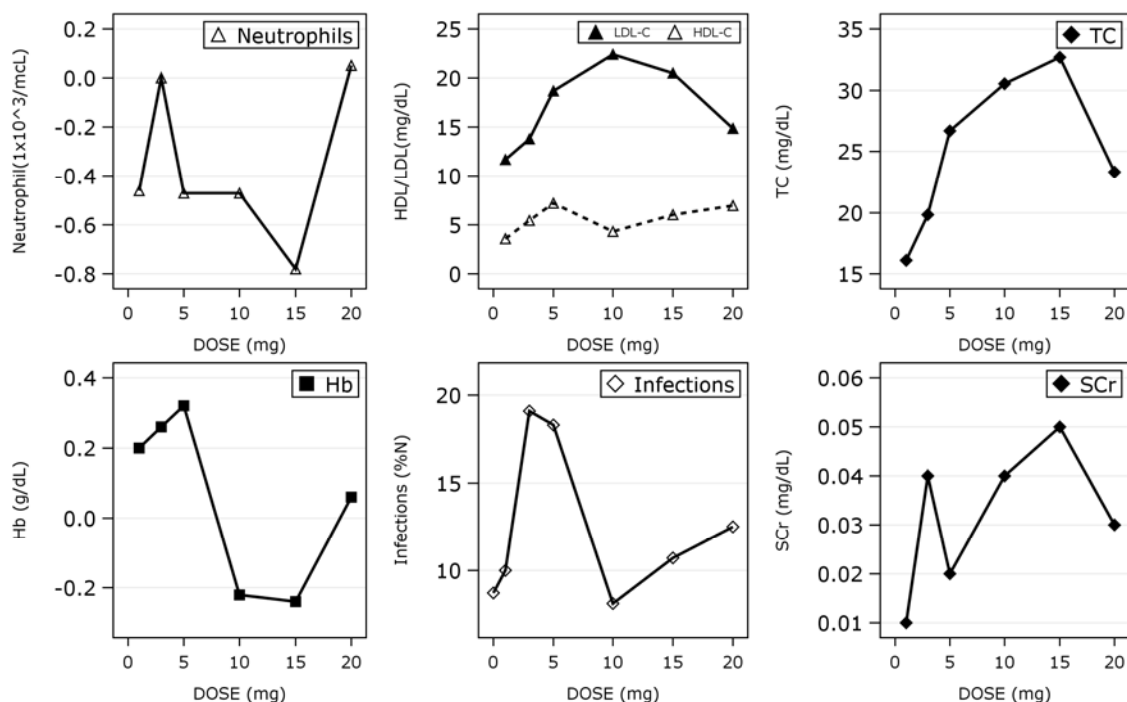
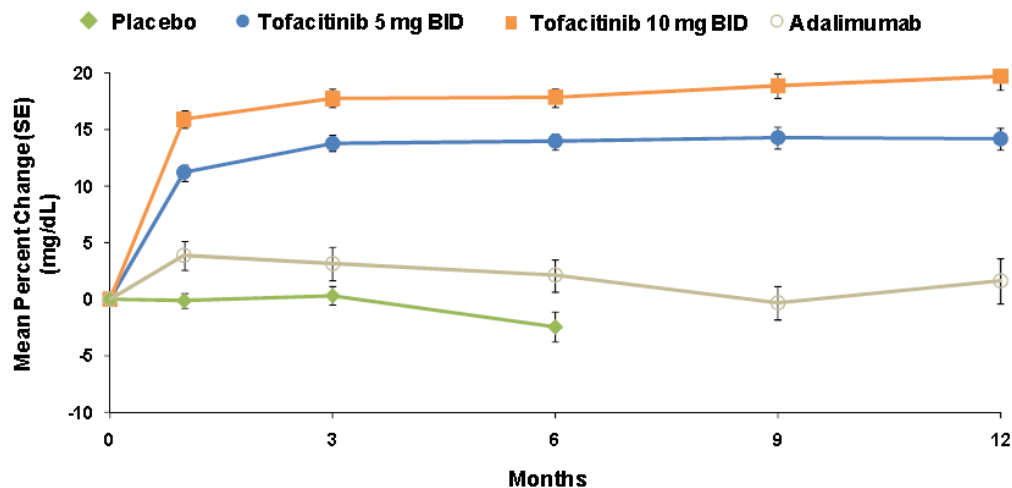


Figure 19: Dose-response relationship for safety endpoints from study 1025. Except infections all other endpoints are shown as placebo adjusted change from baseline to week 12 (delta baseline). Infections are reported as percent incidence at week 12. Except 20 mg QD all other doses were given in BID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

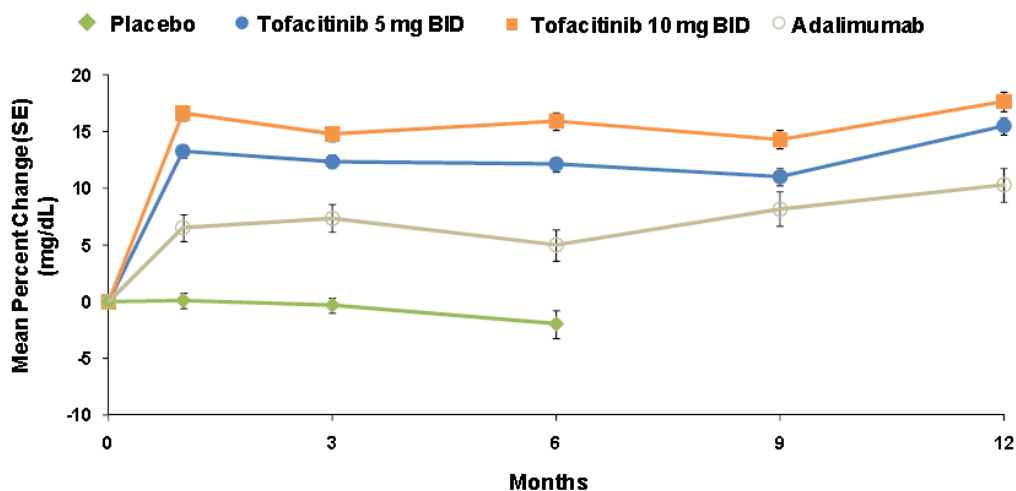


Mean (\pm SE) Percent Change From Baseline in LDL-c (mg/dL) per Visit - All Phase 3 Studies (Overall 0 to 12 Months)

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

Figure 20: Mean (\pm 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)

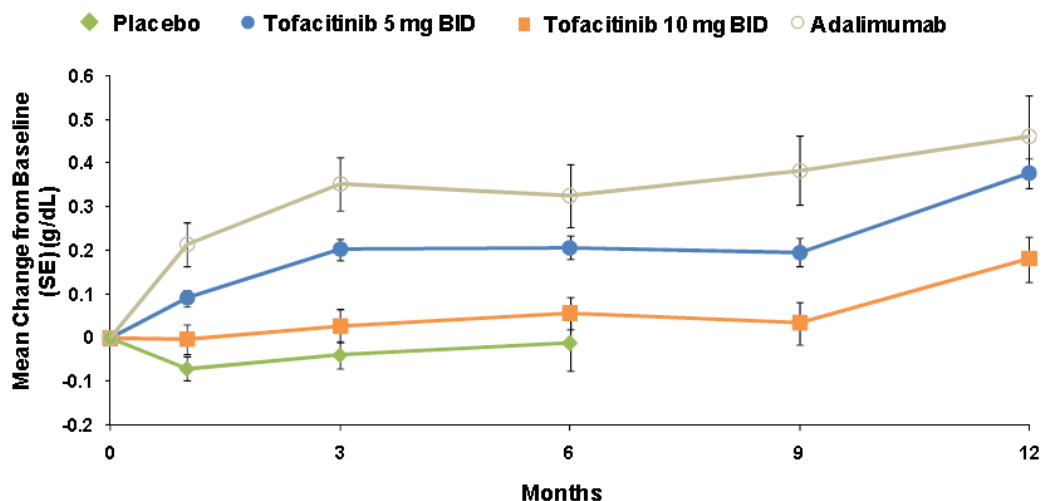


Mean (\pm SE) Percent Change From Baseline in HDL-c (mg/dL) per Visit in Phase 3 Studies (Overall 0 to 12 Months)

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

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

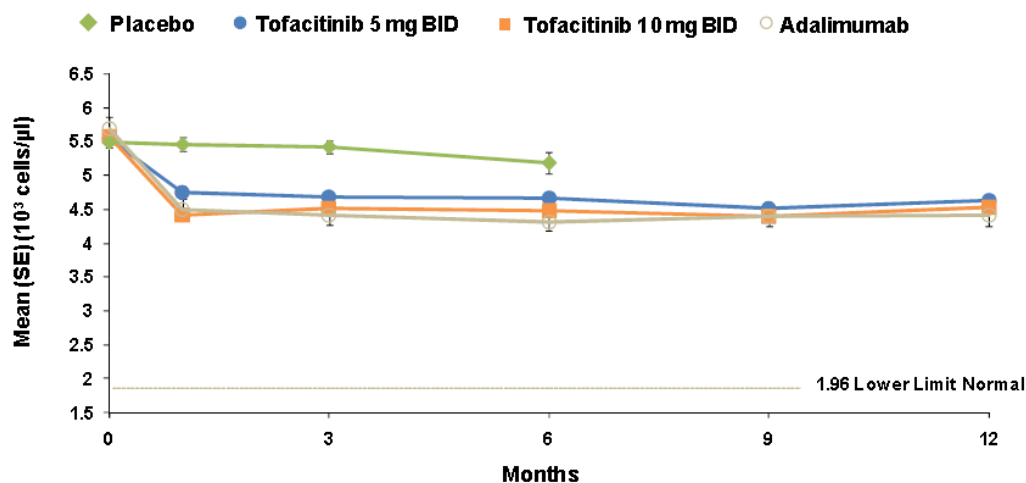
(Source: Figure 49, Pfizer Tofacitinib Advisory Committee Meeting Briefing Document, Dated May 9, 2012)



BID=twice daily, SE=standard error.

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

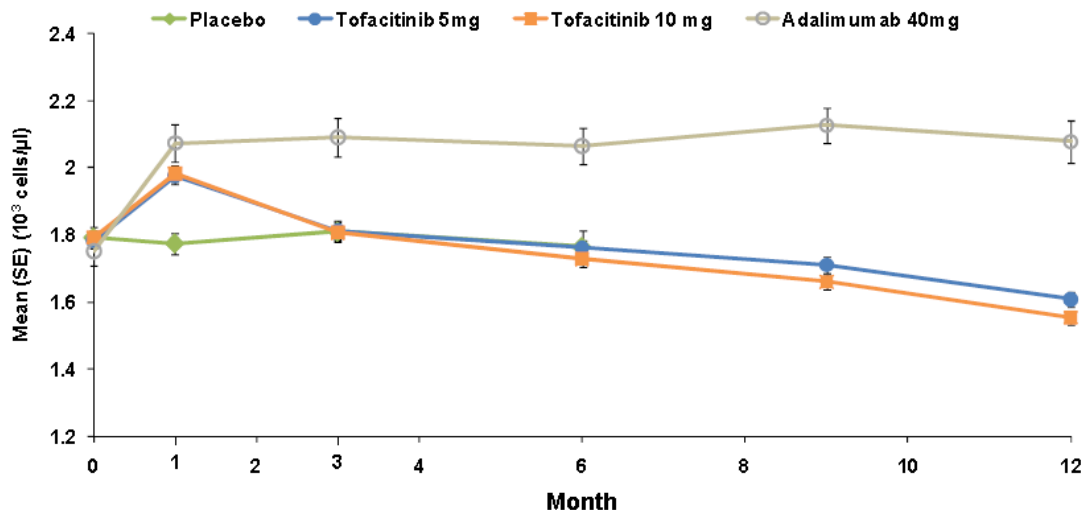
(Source: Figure 52, Pfizer Tofacitinib Advisory Committee Meeting Briefing Document, Dated May 9, 2012)



BID=twice daily, SE=standard error.

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

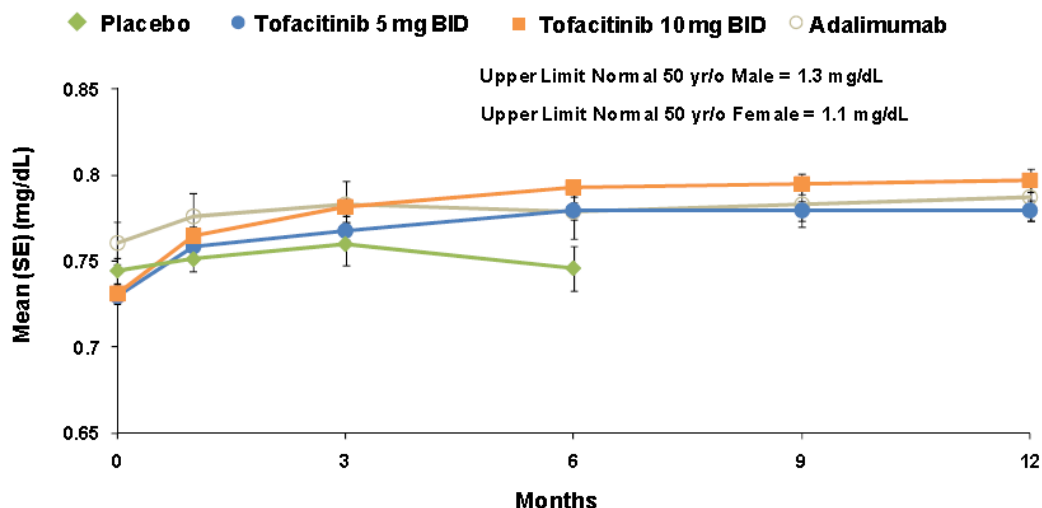
(Source: Figure 53, Pfizer Tofacitinib Advisory Committee Meeting Briefing Document, Dated May 9, 2012)



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 IC_{50} 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.

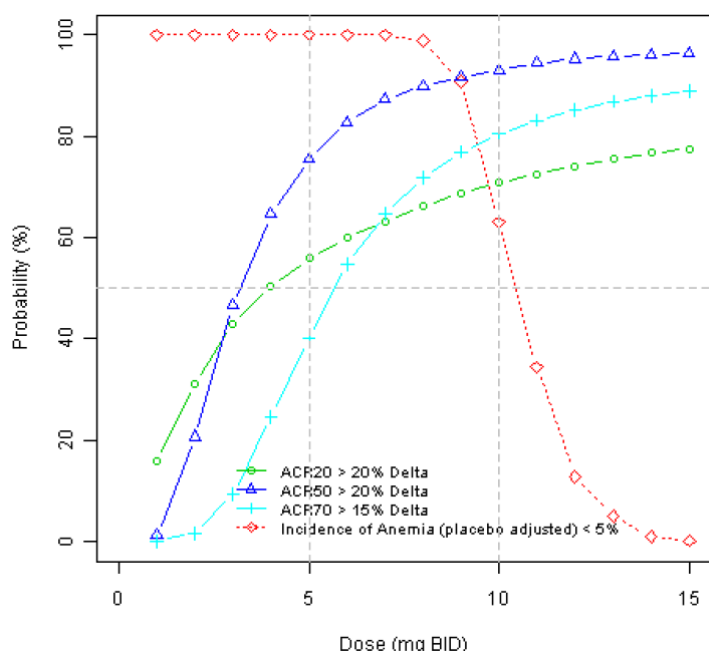


Figure 26: Probability of Achieving Target Effects for Efficacy (ACR20, ACR50 and ACR70 Response Rates) and Safety (Anemia) Endpoints Based on Dose-Response Modeling of A3921025 Data

(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.

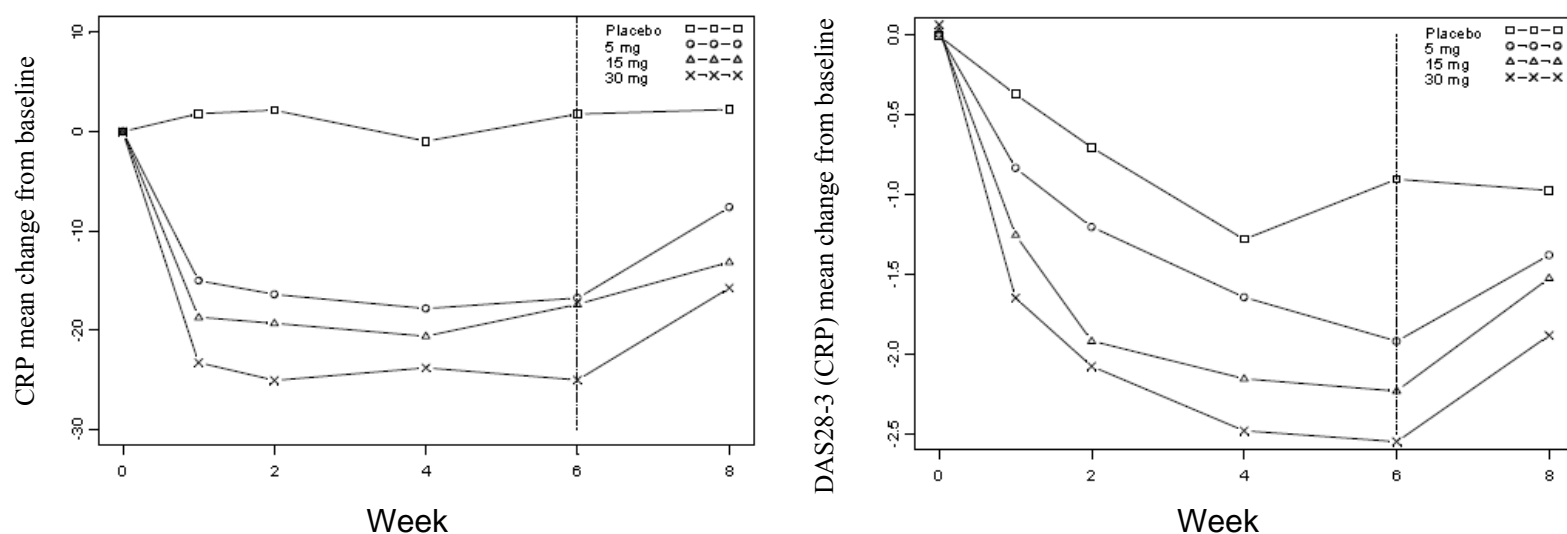


Figure 27: Time Course of Changes in CRP and DAS28-3(CRP) in Study A3921019

(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 rationale 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 arthritis³. 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- γ 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 (

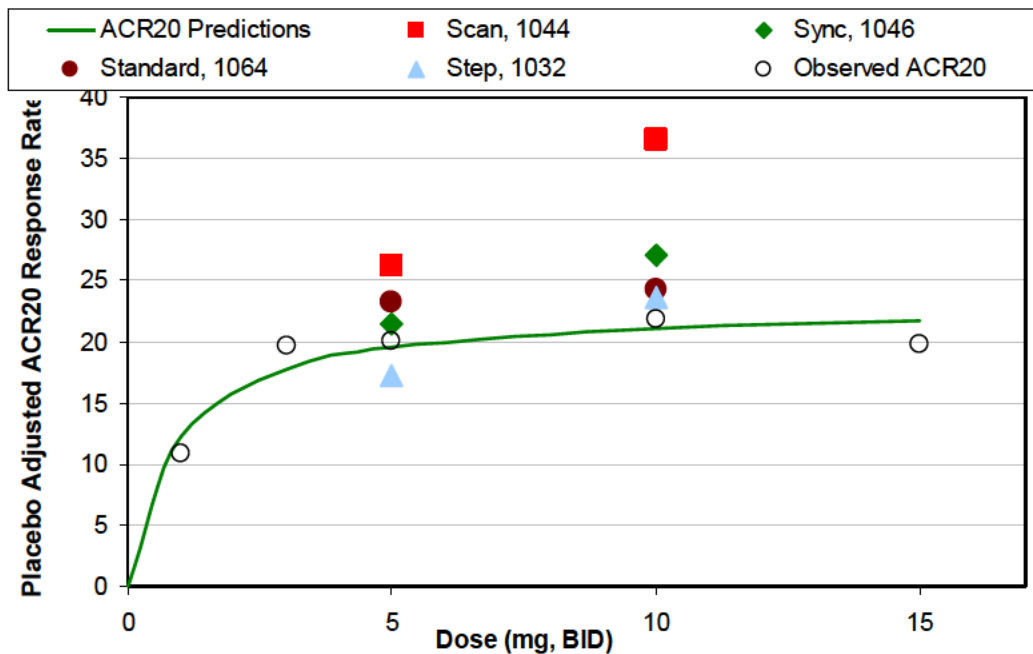
Figure 28, Figure 29 and

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).

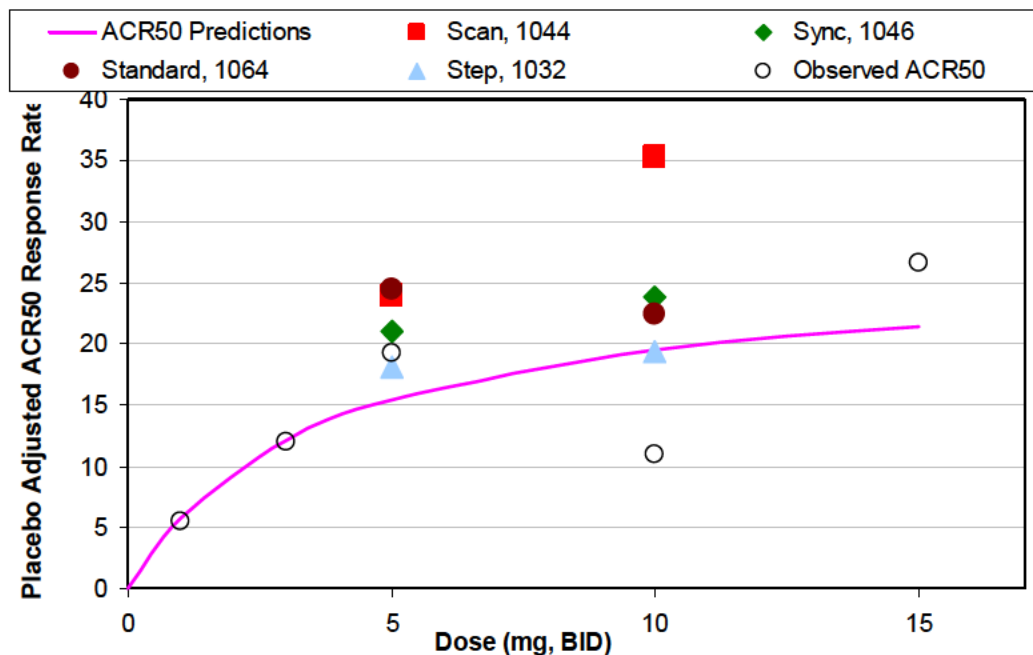
Among other safety markers, in Phase 3 trials, dose-dependent changes were seen in LDLC, HDLC, serum creatinine and neutrophil counts which were consistent with the trends observed in Phase 2 studies.

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.



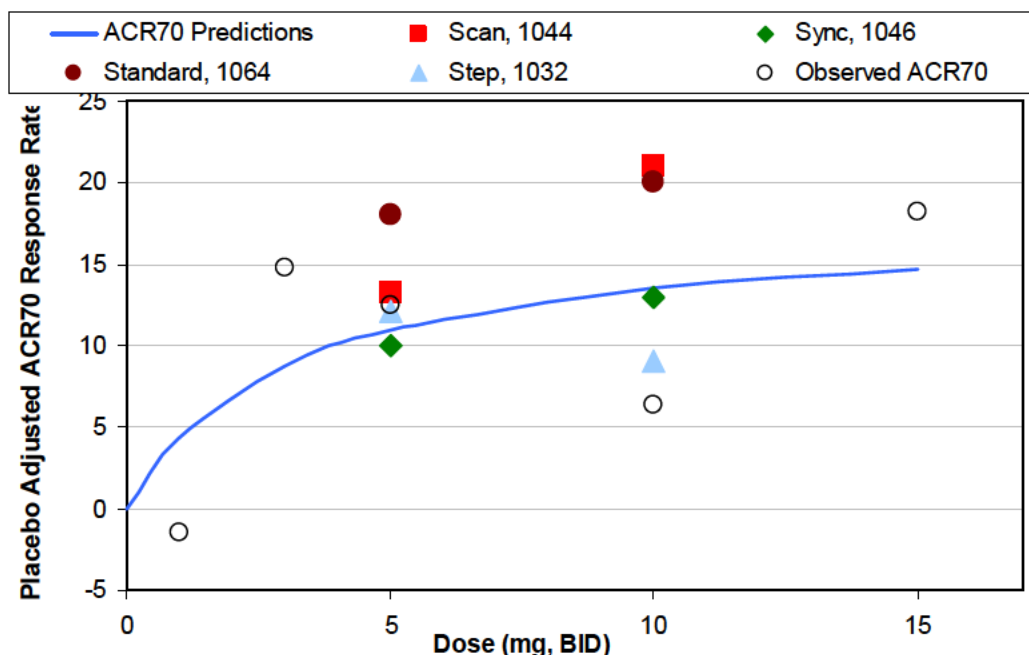
(Primary time point is Month 6 for Scan (A3921044), Sync (A3921046) and Standard (A3921064) studies and Month 3 for the Step (A3921032) study)

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).

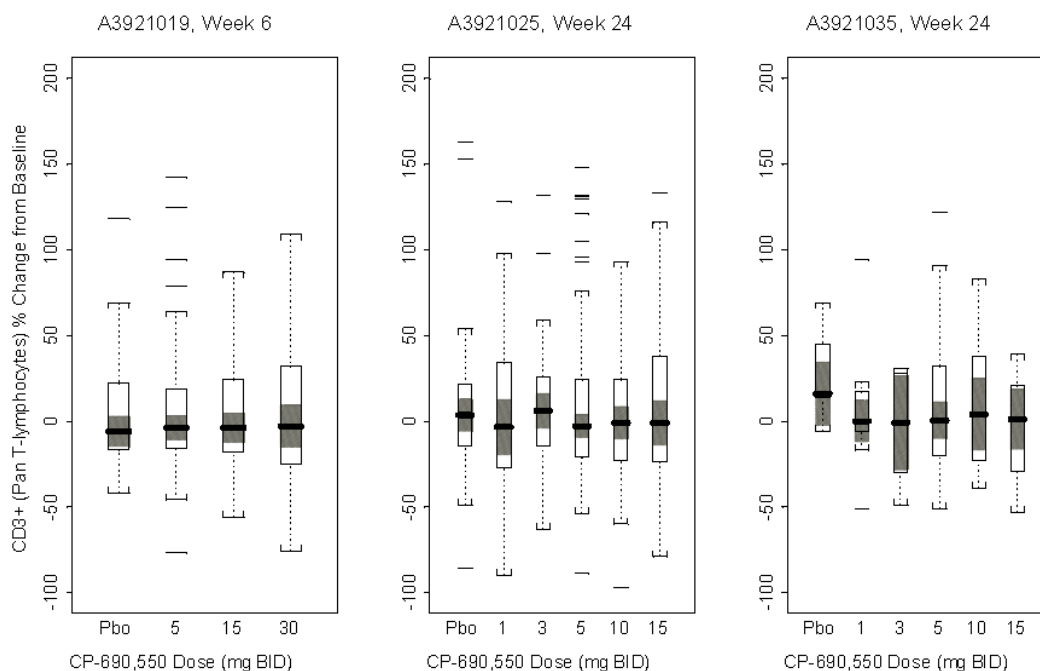


Figure 31: Percent change from baseline in CD3+ counts in RA patients

(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.

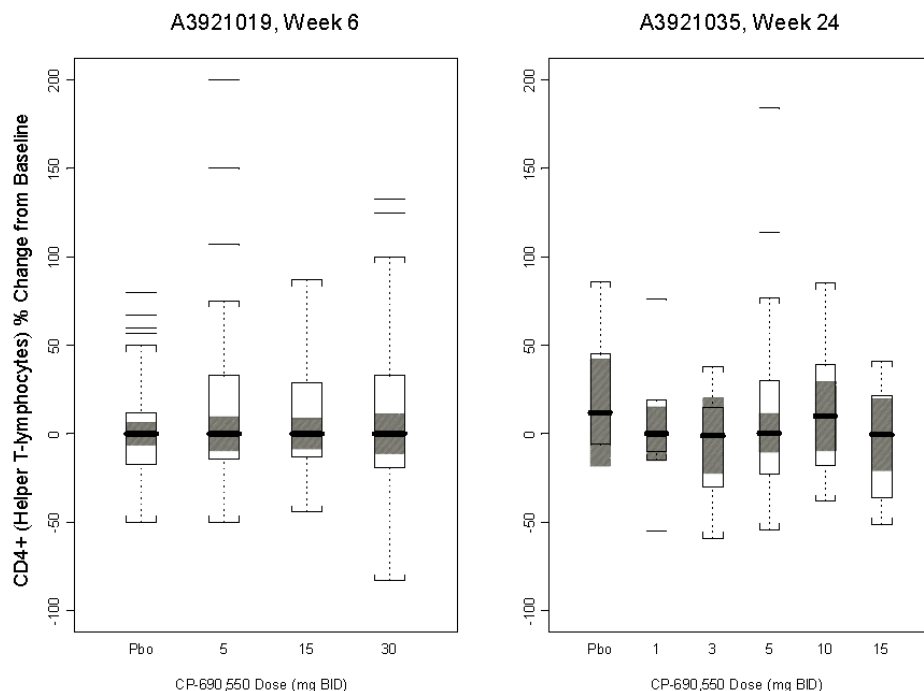


Figure 32: Percent change from baseline in CD4+ counts in RA patients

(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).

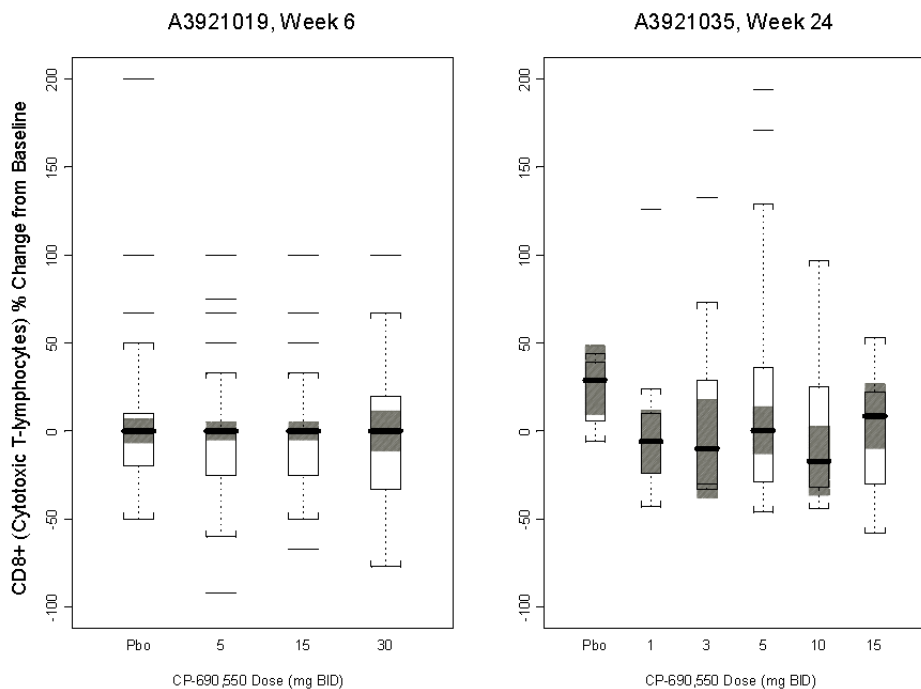


Figure 33: Percent change from baseline in CD8+ counts in RA patients

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

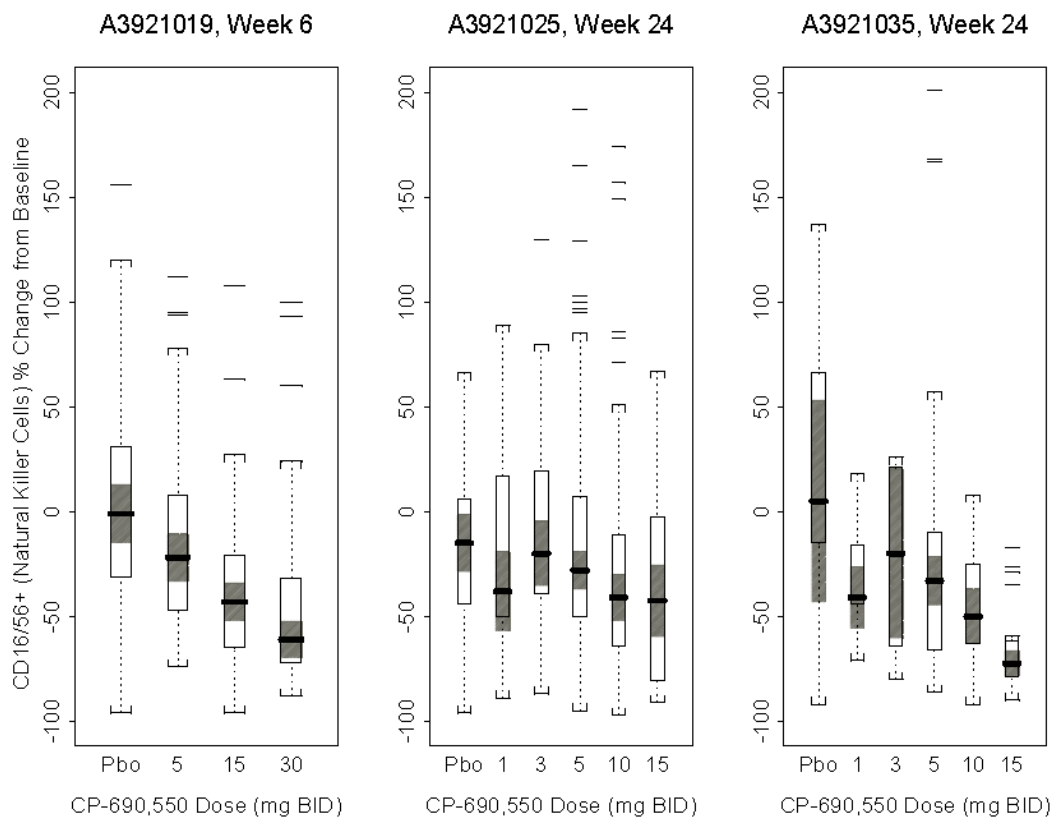


Figure 34: Percent change from baseline in CD16/56+ counts in RA patients

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

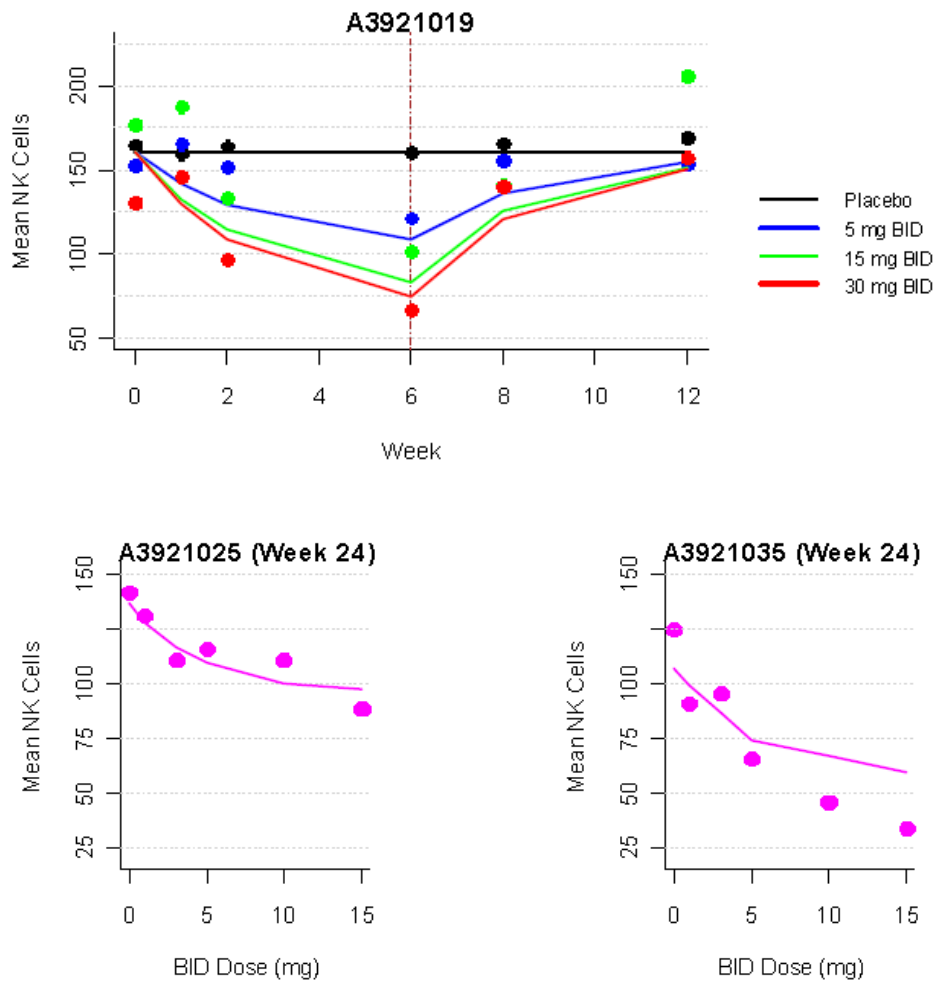


Figure 35: Observed mean CD16/56+ counts (Filled Circles) and Model Predictions (Lines) from Final Dose-Response Model for trial A3921019, A3921025 and A3921035

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

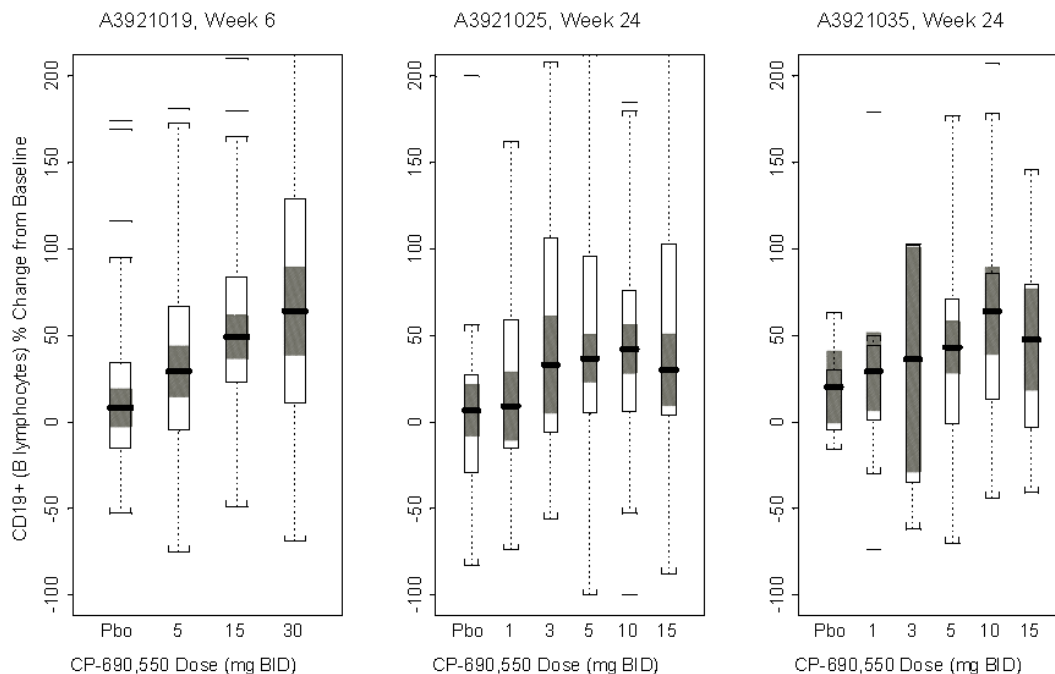


Figure 36: Percent change from baseline in CD19+ counts in RA patients

(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.

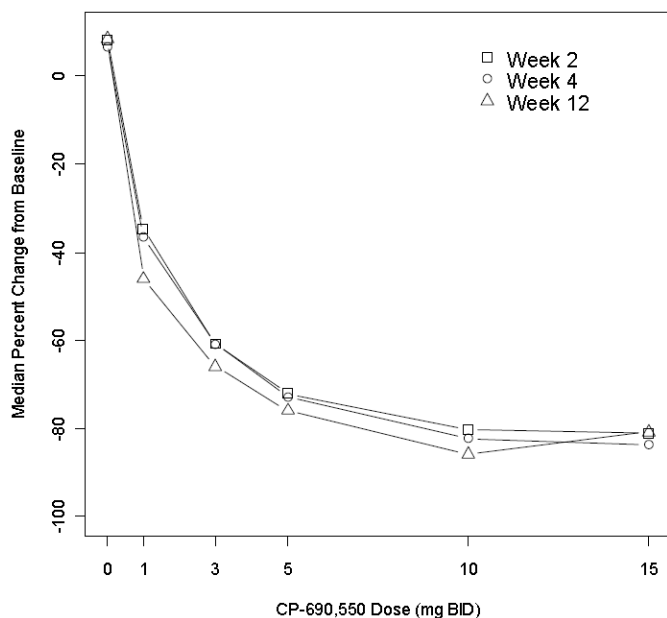


Figure 37: Effect of CP-690,550 on CRP in RA Patients Based on Pooled Analysis of Phase 2 Studies A3920125, A3921035, A3921039 and A3921040

(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).

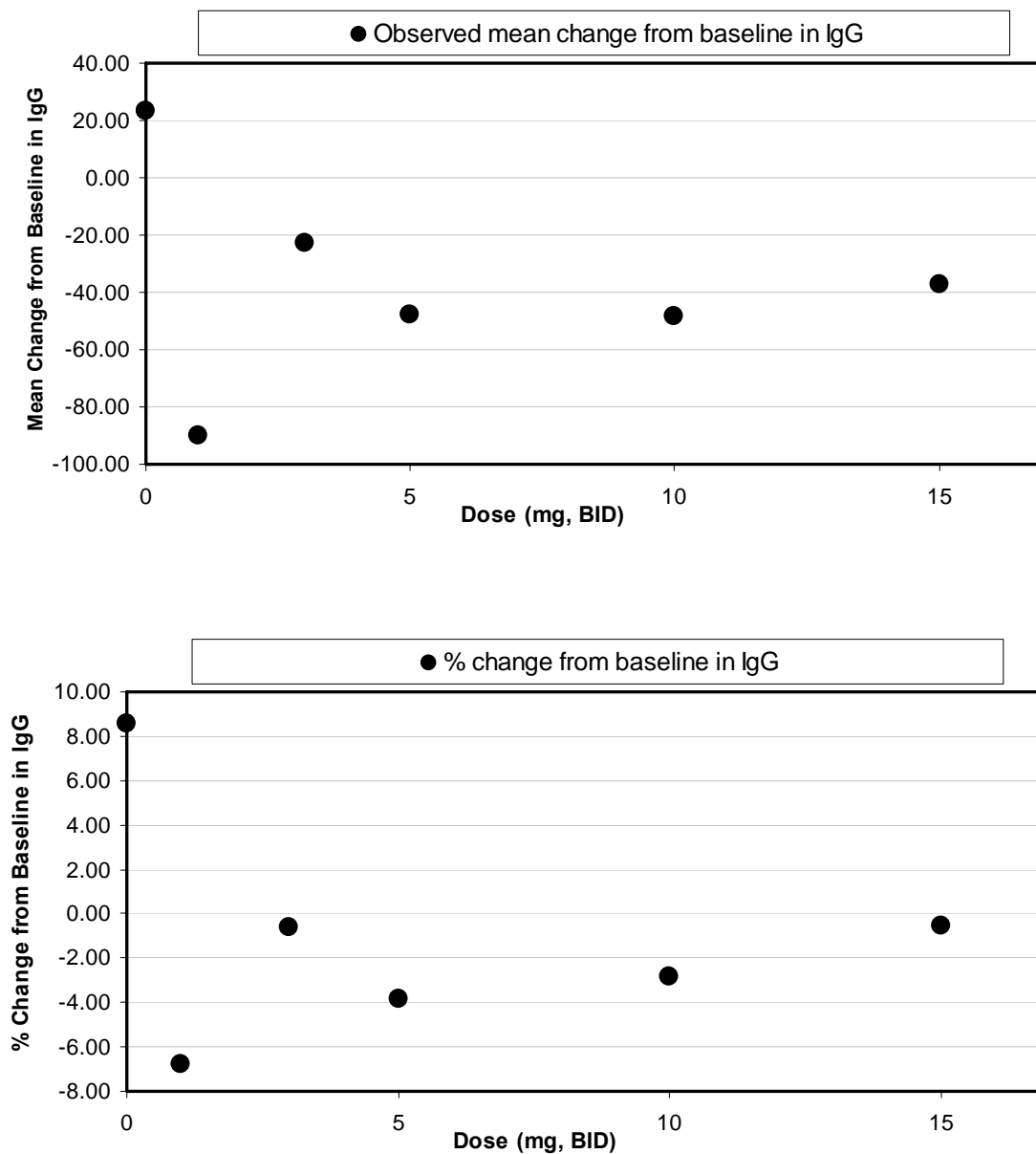


Figure 38: Mean observed and percent change (top and bottom figure, respectively) from baseline in total serum IgG following 24 week treatment with tofacitinib in study A3921025

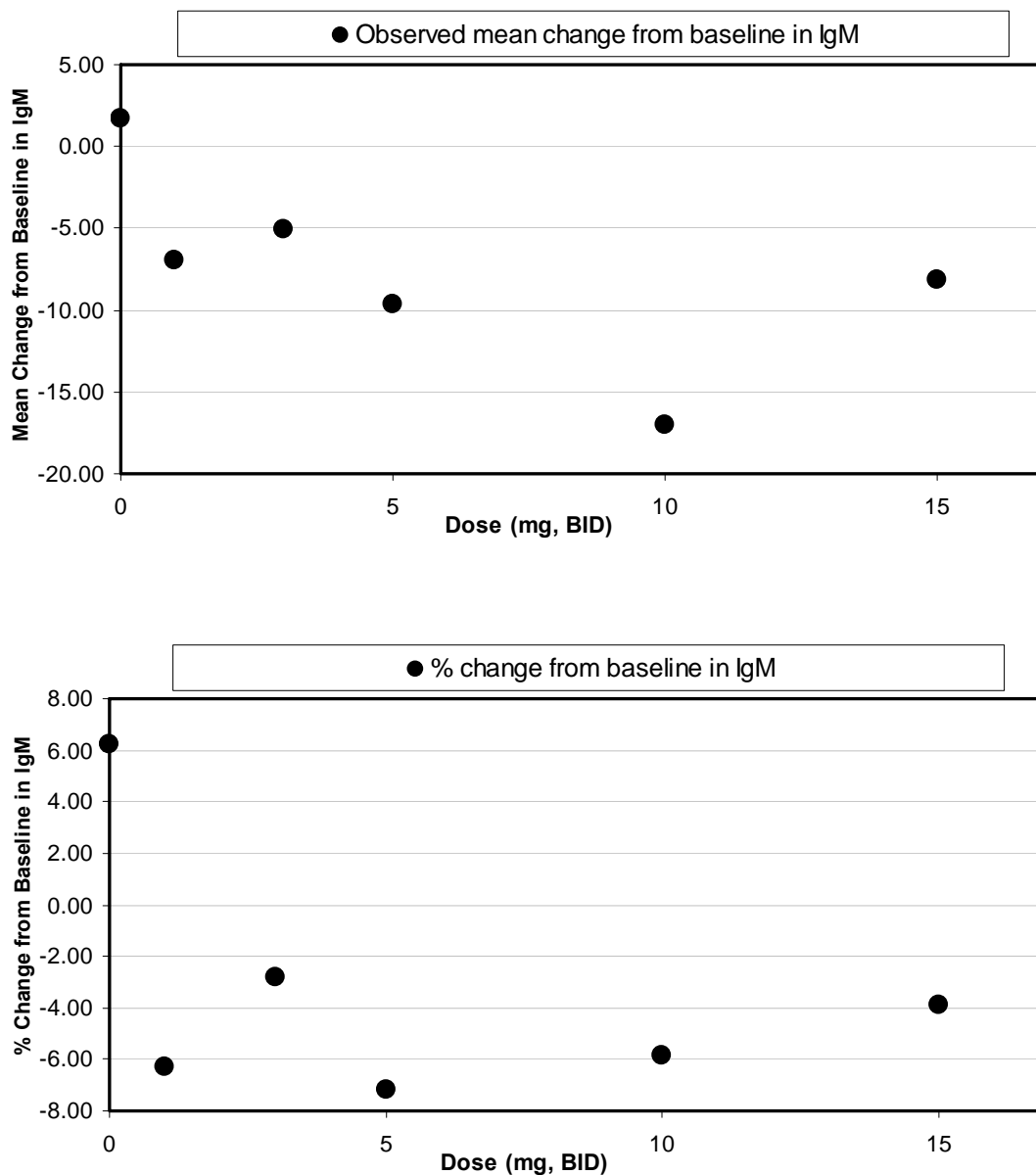


Figure 39: Mean observed and percent change (top and bottom figure, respectively) from baseline in total serum IgM following 24 week treatment with tofacitinib in study A3921025

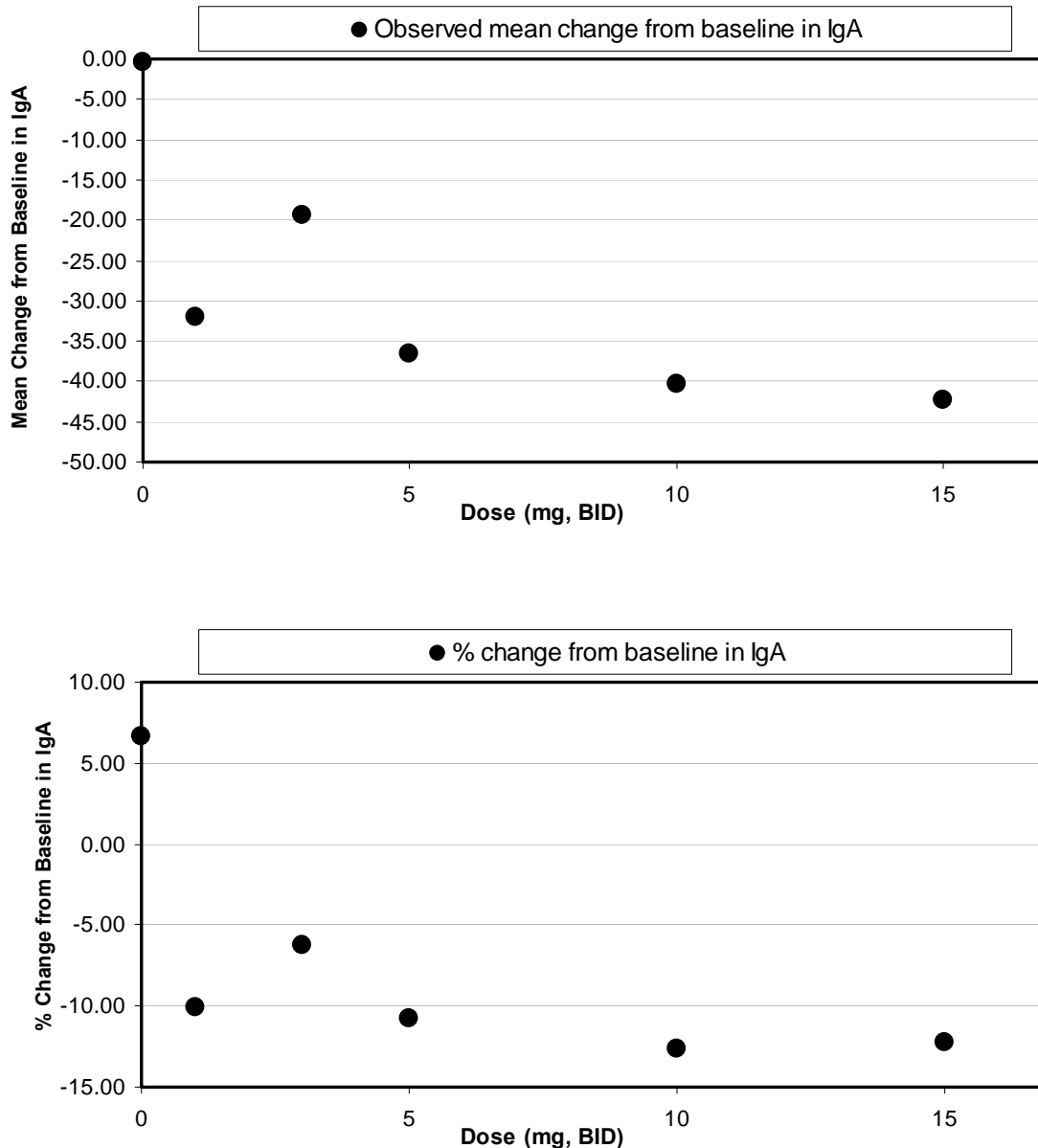


Figure 40: Mean observed and percent change (top and bottom figure, respectively) from baseline in total serum IgA following 24 week treatment with tofacitinib in study A3921025

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

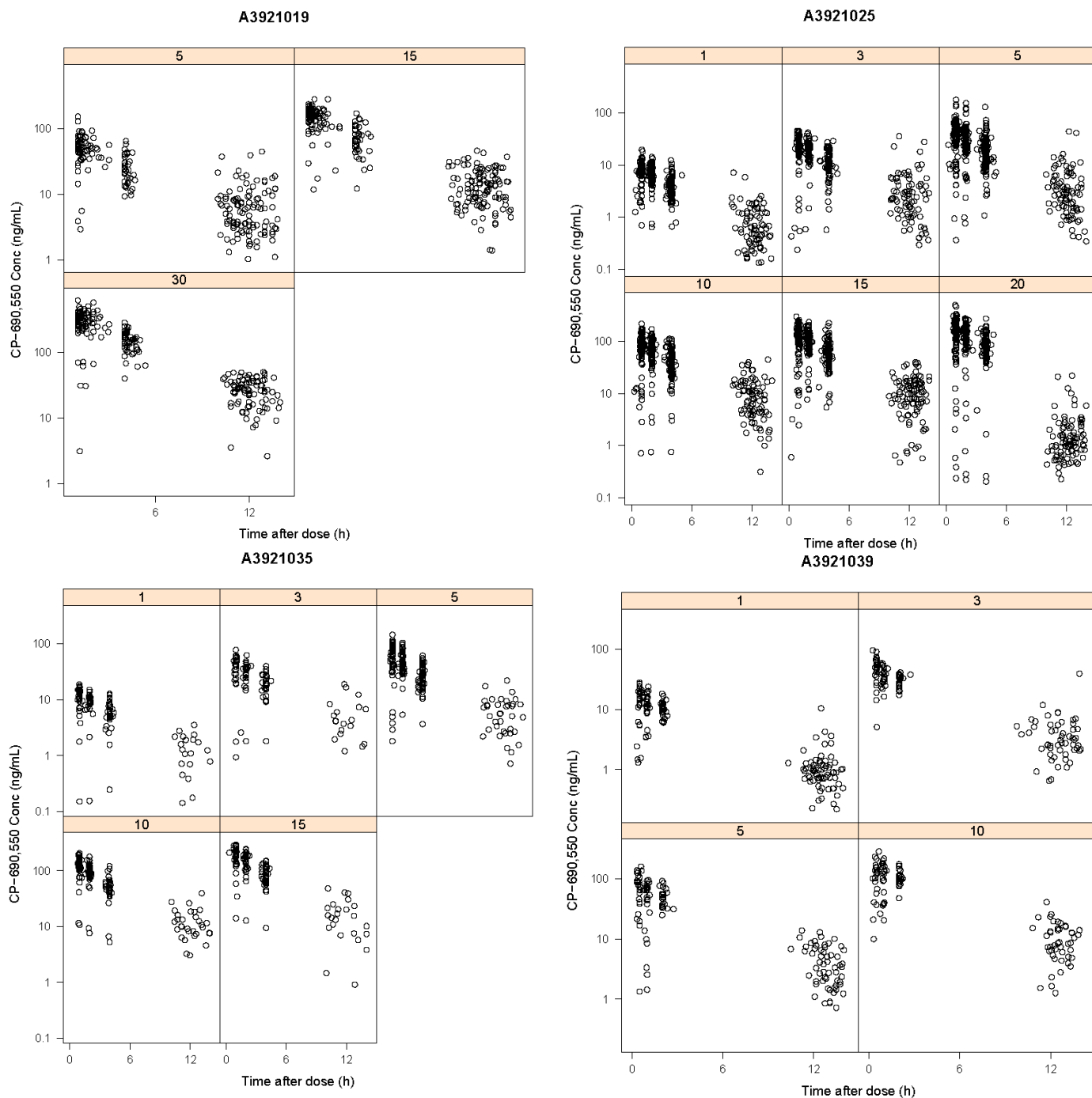


Figure 41: Observed CP-690,550 Concentrations versus Actual Time After Dose. Plots are presented for each study, stratified by CP-690,550 dose (mg)

(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				
$\Omega_{CL/F}^2$	0.0951	10.5		
$\Omega_{CL/F-V/F}^2$	0.0357	26.3		
$\Omega_{V/F}^2$	0.0905	11.2		
Inter-occasion Variance				
Ω_{F1}^2	0.0524	19.3		
Residual Variance				
σ_{prop}^2	0.118	6.64		
$\sigma_{prop,trough}^2$	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

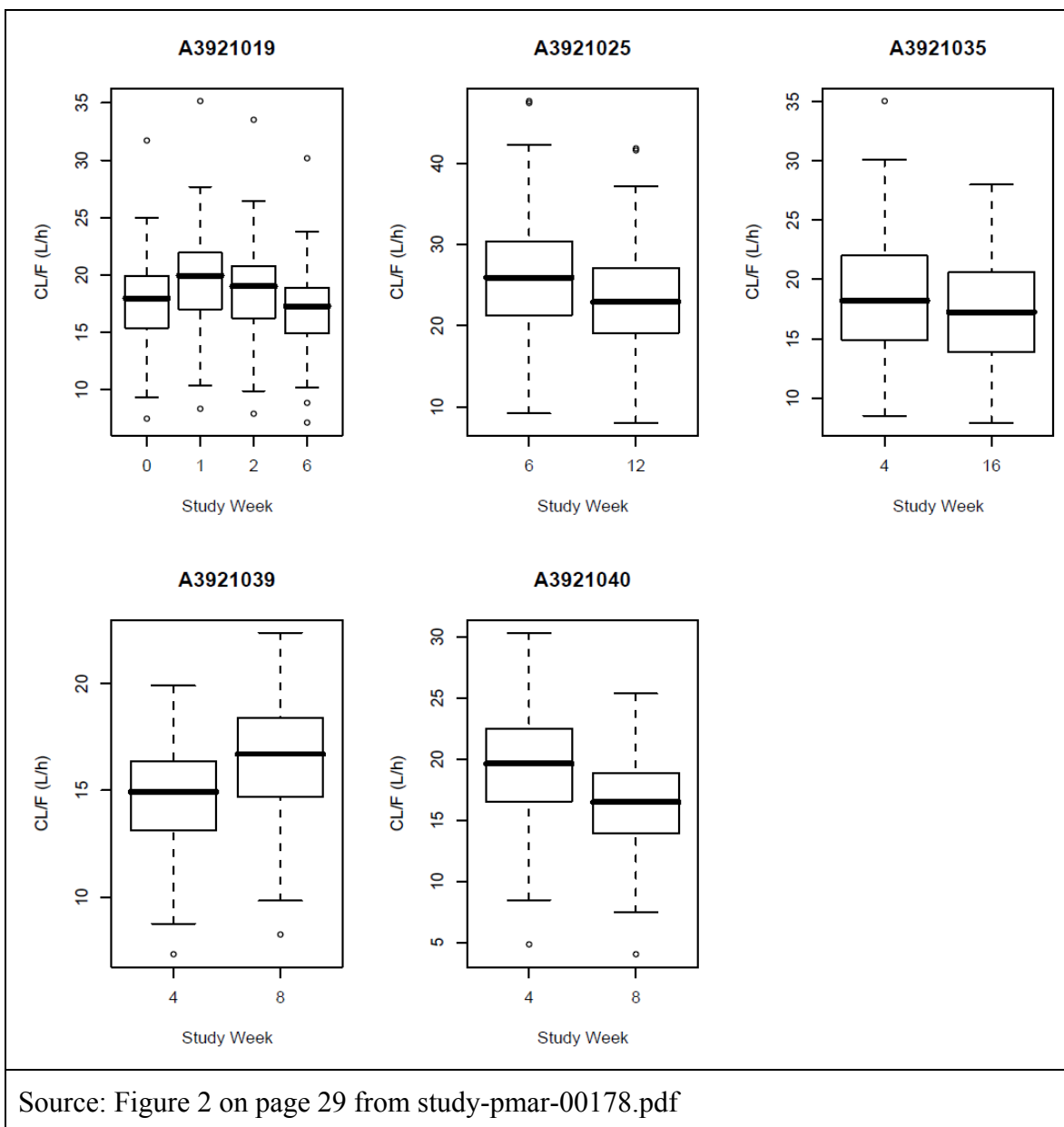


Figure 42: CL/F empirical Bayes estimates vs. Study Week for the CP-690,550 Base Model

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:

$$\frac{CL}{F_i} = \theta_{CL} \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})} \right)^{\theta_4} \cdot \left(\frac{AGE_i(\text{years})}{55(\text{years})} \right)^{\theta_7} \cdot \theta_7^{\text{Female}} \\ \cdot \theta_9^{\text{AfricanAmerican}} \cdot \theta_{10}^{\text{Asian}} \cdot \theta_{11}^{\text{Hispanic}} \cdot \theta_{12}^{\text{OtherRace}} \cdot \theta_{14}^{\text{A3921025}} \cdot \exp^{\eta_{CL/Fi}}$$

CRCL < 80 mL/min:

$$\frac{CL}{F_i} = \theta_{CL} \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})} \right)^{\theta_4} \cdot \left(\frac{AGE_i(\text{years})}{55(\text{years})} \right)^{\theta_7} \cdot \left(\frac{CRCL_i(\text{mL/min})}{80(\text{mL/min})} \right)^{\theta_{17}} \cdot \theta_7^{\text{Female}} \\ \cdot \theta_9^{\text{AfricanAmerican}} \cdot \theta_{10}^{\text{Asian}} \cdot \theta_{11}^{\text{Hispanic}} \cdot \theta_{12}^{\text{OtherRace}} \cdot \theta_{14}^{\text{A3921025}} \cdot \exp^{\eta_{CL/Fi}}$$

$$\frac{V}{F_i} = \theta_{VF} \cdot \left(\frac{WT_i(\text{kg})}{70(\text{kg})} \right)^{\theta_{15}} \cdot \left(\frac{AGE_i(\text{years})}{55(\text{years})} \right)^{\theta_8} \cdot \exp^{\eta_{V/Fi}}$$

$$D1 = \theta_{D1}$$

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

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					
$\Omega_{CL/F}^2$	0.0707	16.0	(0.0558, 0.0931)		
$\Omega_{CL/F-V/F}^2$	0.0112	86.3	(0.00052, 0.0314)		
$\Omega_{V/F}^2$	0.0674	13.7	(0.0518, 0.0807)		
Inter-occasion Variance					
Ω_{F1}^2	0.0528	20.8	(0.0371, 0.0878)		
Residual Variance					
σ_{prop}^2	0.118	6.57	(0.106, 0.132)		
$\sigma_{prop, trough}^2$	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

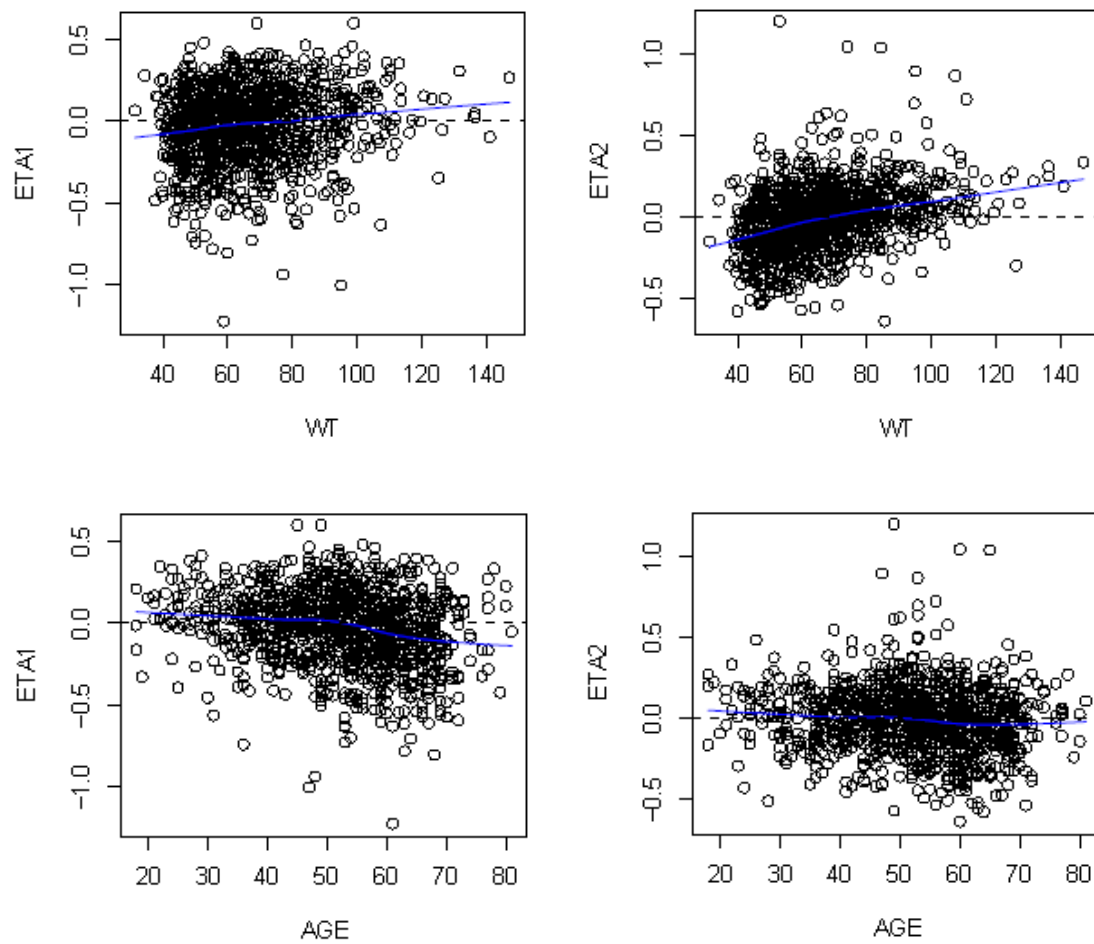


Figure 43: Relationship of variability on CL/F (ETA1) and variability on V/F (ETA2) with weight and age (Base model)

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 AUC_{ss} and C_{max,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:

$$\frac{CL}{F_{140kg,i}} = \frac{CL}{F_i} \cdot \left(\frac{140kg}{70kg} \right)^{\theta_{CL,i}}$$

$$\frac{V}{F_{140kg,i}} = \frac{V}{F_i} \cdot \left(\frac{140kg}{70kg} \right)^{\theta_{V,i}}$$

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.

$$AUC_{ss, 140kg, i} = \frac{Dose \cdot 1000}{\frac{CL}{F_{140kg,i}}}$$

$$C_{max,ss, 140kg, i} = \frac{k_0 \cdot 1000}{k_e \cdot \frac{V}{F_{140kg,i}}} \cdot \frac{1 - \exp^{-k_e \cdot D1}}{1 - \exp^{-k_e \cdot \tau}}$$

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

$$\frac{CL}{F_{female,i}} = \frac{CL}{F_i} \cdot \theta_{CL,i}^{female}$$

$$\frac{V}{F_{female,i}} = \frac{V}{F_i} \cdot \theta_{CL,i}^{female}$$

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.

$$AUC_{ss, \text{female}} = \frac{\text{Dose} \cdot 1000}{\frac{CL}{F_{\text{female},i}}}$$

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

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 C_{\max} is shown in Figure 44. Also shown are recommendations for dose adjustments.

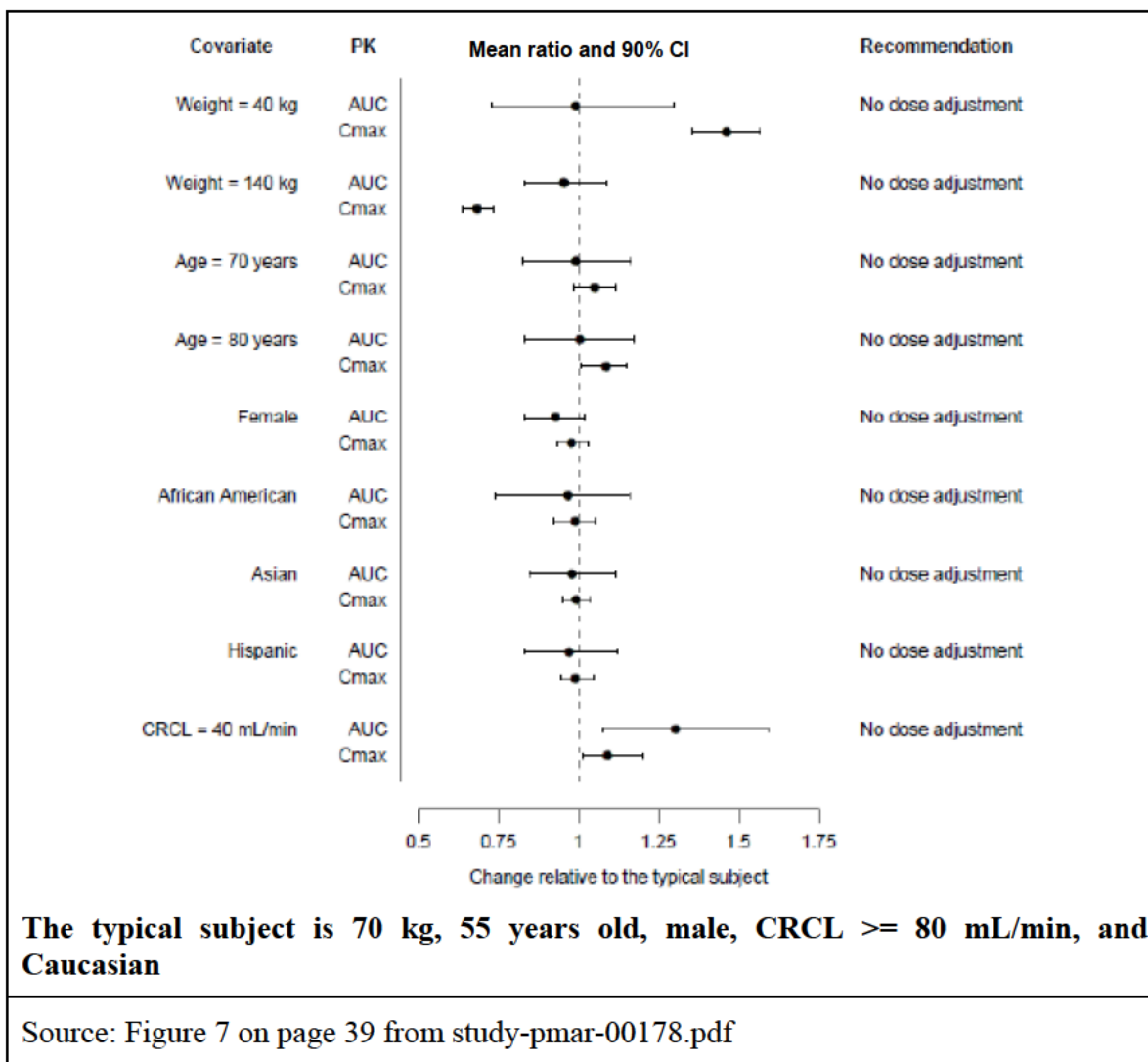


Figure 44: Impact of Covariates on the Pharmacokinetics of CP-690,550

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 C_{ave} 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

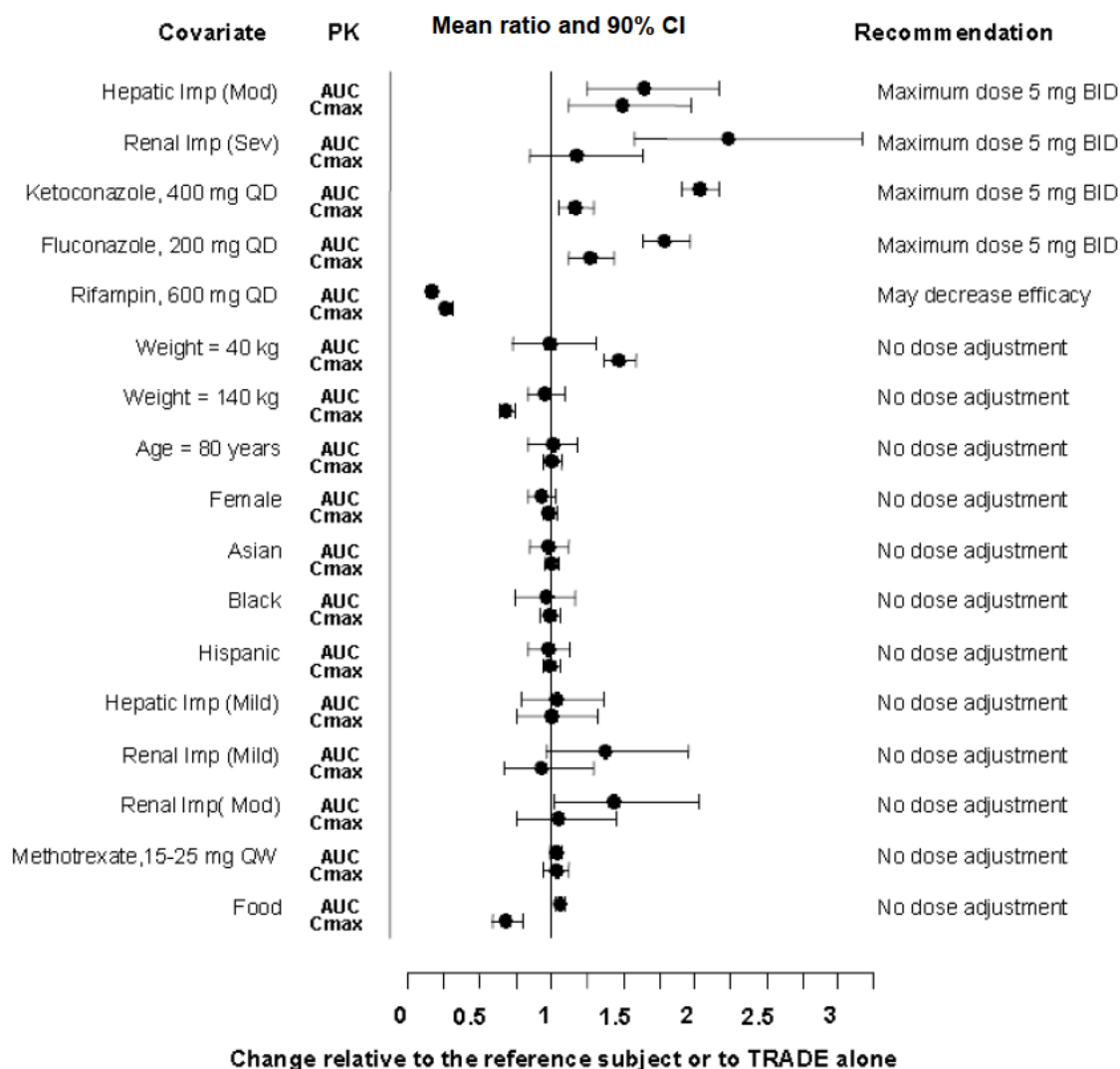
4.1. Introduction

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	\\Cdsub1\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 C_{max} metrics was assessed based on bootstrap outputs using the steps outlined under heading "assessment of impact of covariates on AUC_{ss} and C_{max,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 C_{\max} 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 C_{\max} 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 AUC_{ss} and $C_{\max,ss}$ based on output from bootstrap analysis

Covariate comparison (Test vs. Reference)	AUC _{ss}		C _{max,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)

**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 C_{max} 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

Parameter, units	Summary Statistics ^a by Genotype			Individual Values ^b for Ultra Extensive Metabolizers (N=2)
	All Subjects (N=60)	Extensive Metabolizers (N=52)	Poor Metabolizers (N=6)	
AUC _{last} , ng.hr/mL	2670 (28)	2670 (28)	3114 (12)	2180, 1280
AUC _{inf} , ng.hr/mL	2683 (28)	2683 (28)	3130 (12)	2190, 1290
C _{max} , ng/mL	564 (34)	565 (31)	647 (41)	530, 227
T _{max} , hr	1.0 (0.3-4.1)	1.0 (0.3-4.1)	0.5 (0.3-4.0)	2.0, 2.0
t _{1/2} , 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

^aGeometric mean (%CV) for AUC and C_{max}; median (range) for T_{max}; arithmetic mean (%CV) for t_{1/2}.

^bParameter 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

(b) (4)

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

- **Objective:** To investigate whether (b) (4) is a human P-glycoprotein (P-gp) substrate
- **Method:** Bidirectional transport of the (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 (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 (b) (4) through control MDCKII cells and MDR transfected MDCKII-MDR1 monolayers in time is shown in Figure 46. The ratio of (b) (4) efflux in MDCKII-MDR1 cells and MDCKII parental cells is shown in Table 34, which was approximately 11-12. Efflux of (b) (4) tested at 12 μM concentration, was abolished in the presence of either ketoconazole or verapamil (Table 35).

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

Concentration (b) (4) (μM)	Efflux ratio MDCKII- MDR1 cells (\pm SD)	Efflux ratio MDCKII parental cells (\pm SD)	$\text{ER}_{\text{MDR1}}/\text{ER}_{\text{MDCKII}}$ (\pm SD)
3	18.43 (\pm 0.08)	1.64 (\pm 0.11)	11.22 (\pm 0.07)
12	21.17 (\pm 0.21)	1.85 (\pm 0.29)	11.44 (\pm 0.16)
102	10.43 (\pm 0.05)	0.87 (\pm 0.12)	11.97 (\pm 0.14)

Table 35: Inhibition of efflux of (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} ($\times 10^{-6} \text{ cm/s}$) (n=3)(\pm SD)	Mean B-A P_{app} ($\times 10^{-6} \text{ cm/s}$) (n=3)(\pm SD)	ER (\pm SD)	Mean A-B Recovery (percent) (n=3)(\pm SD)	Mean B-A Recovery (percent) (n=3)(\pm SD)
Ketoconazole	8.88 (\pm 1.14)	8.61 (\pm 2.01)	0.97 (\pm 0.21)	97 (\pm 3)	97 (\pm 6)
Verapamil	5.21 (\pm 1.09)	7.64 (\pm 0.83)	1.50 (\pm 0.23)	105 (\pm 11)	98 (\pm 4)

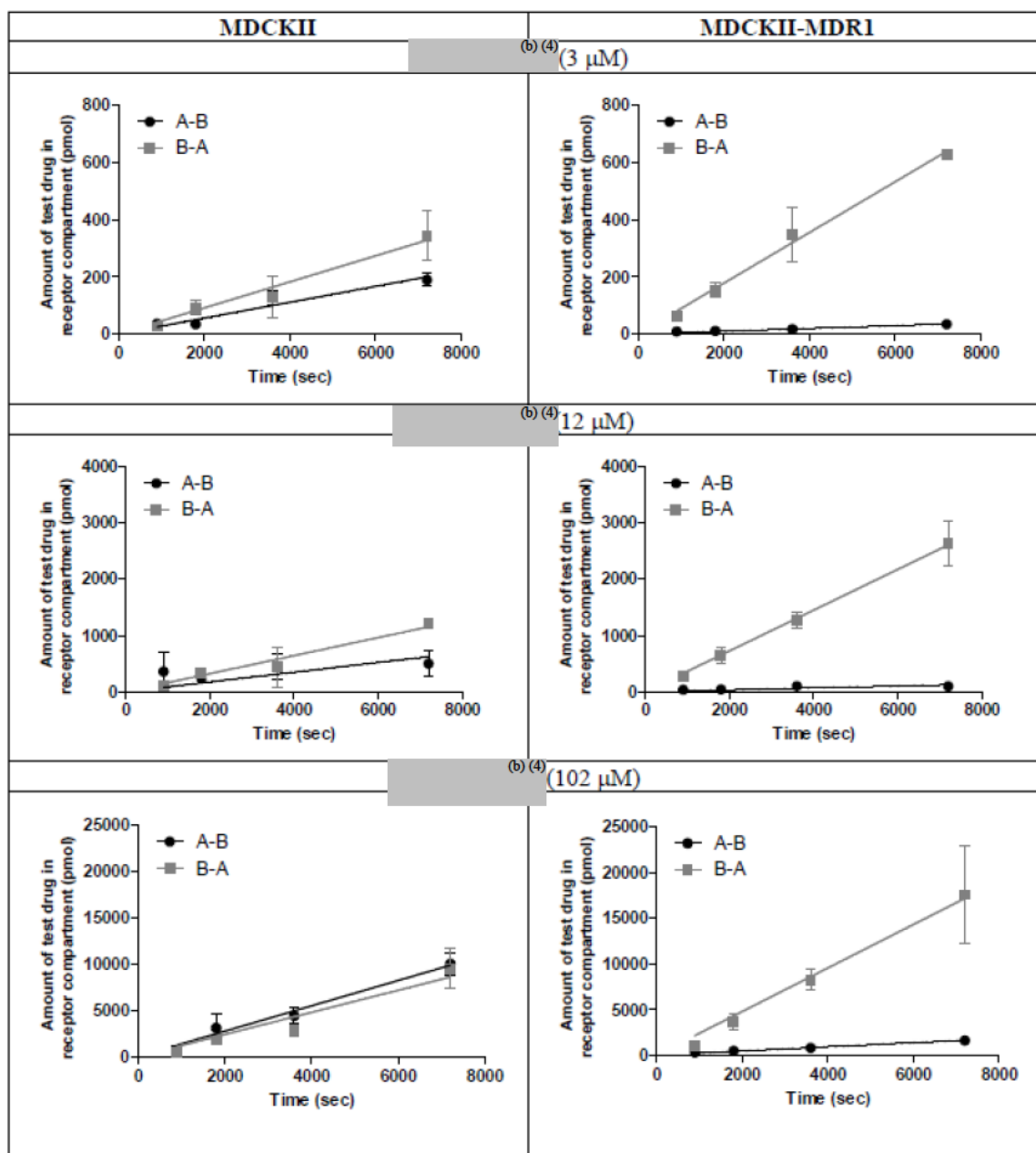


Figure 46: Bidirectional transport of (b) (4) through MDCKII and MDCKII-MDR1 monolayers in time

- **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 (b) (4) (CP-690550) in CACO-2 cells

- **Objective:** To investigate whether (b) (4) inhibits the transport of [³H]-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 (b) (4)
- **Results:** (b) (4) is a low potency inhibitor of digoxin flux in Caco-2 cells, with 72% inhibition at maximum concentration of 1000 μ M. The estimated IC_{50} for (b) (4) against the degree of activity of digoxin flux is 311 μ M (Figure 47).

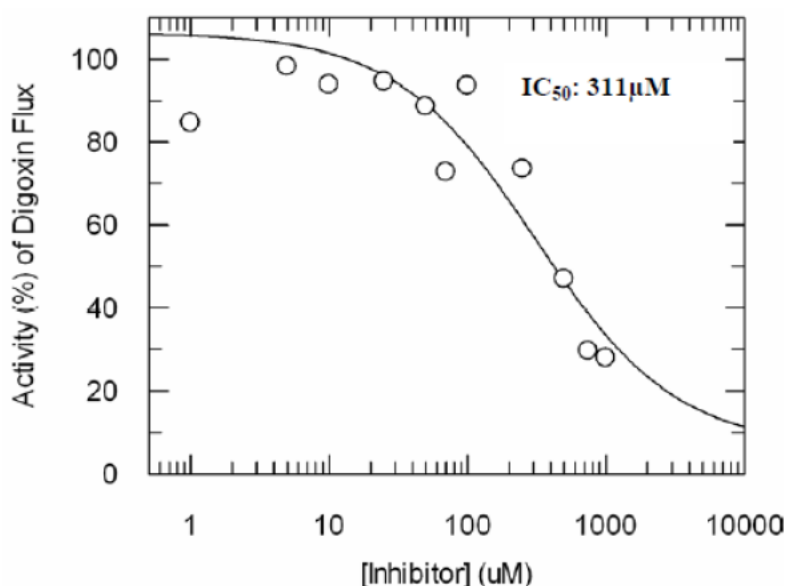


Figure 47: Degree of activity of digoxin flux across Caco-2 cell monolayers in the presence of increasing amounts of (b) (4)

- **Conclusion:** Peak plasma concentration following 10 mg bid multiple-dose administration was approximately 310 nM or 0.310 μ M, suggesting that at clinically relevant concentration (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

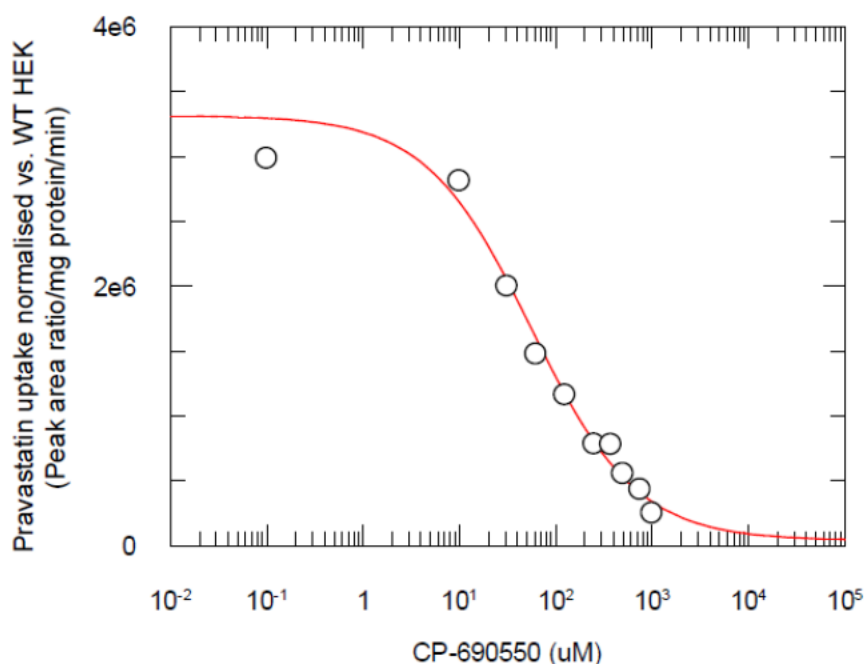
Title: In vitro inhibition of OATP 1B1 by CP-690550

- **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 $\times 10^5$)	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 \pm 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).

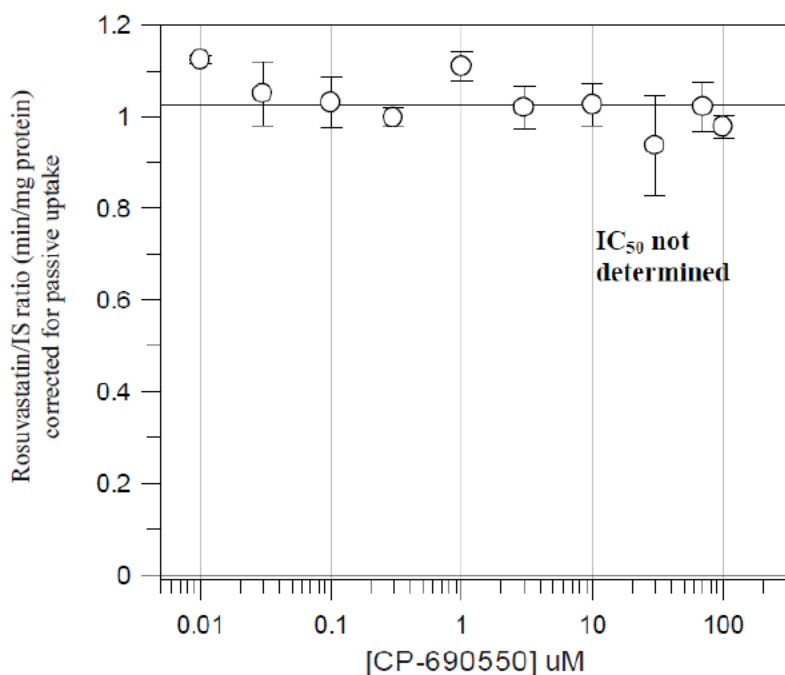


Figure 49: Inhibition of Rosuvastatin Uptake by HEK-OATP 1B3 Cells by CP-690550

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.

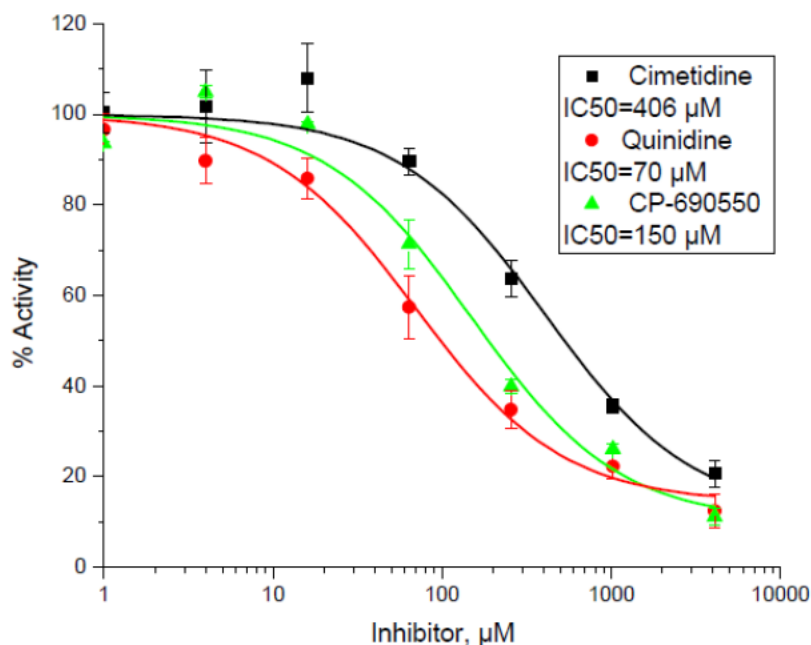


Figure 50: CP-690,550 inhibition of 5 µM Creatinine uptake mediated by hOCT2. Cimetine and Quinidine were used as positive controls. The estimated IC₅₀s for CP-690,550, Cimetine and Quinidine were 150 µM, 406 µM and 70 µM, respectively

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 α 1-Acid Glycoprotein

- **Objective:** To determine the degree of protein binding of CP-690,550 in human serum albumin (HSA) and α 1-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 []	Initial Incubate []	Ultrafiltrate []	Fraction Unbound
(ng/mL)	(ng/mL)	(ng/mL)	
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 []	Initial Incubate []	Ultrafiltrate []	Fraction Unbound
(ng/mL)	(ng/mL)	(ng/mL)	
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 μ M (equivalent to 0.312 μ g/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 μ M. Aliquots 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 μ M. 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 incubations. 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

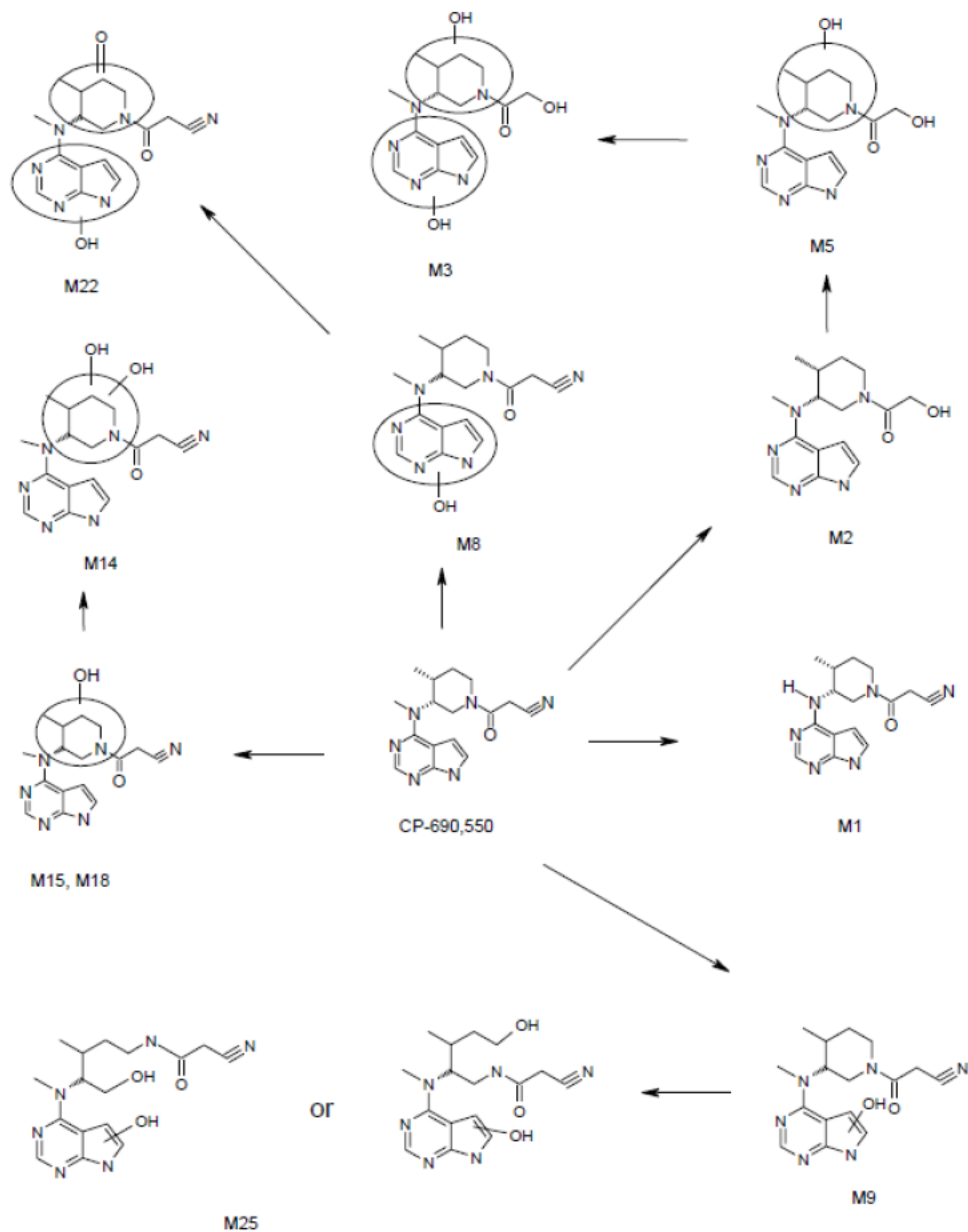


Figure 51: Proposed in vitro metabolic pathways of CP-690,550

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 μ M for 1A2), sulfaphenazole (10 μ M for 2C9), quinidine (1 μ M for 2D6), (+)N-3-benzylrivanol (10 μ M for 2C19), and ketoconazole (1 μ M 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 μ M) indicating that CYP3A was primarily responsible for metabolism of CP-690,550.

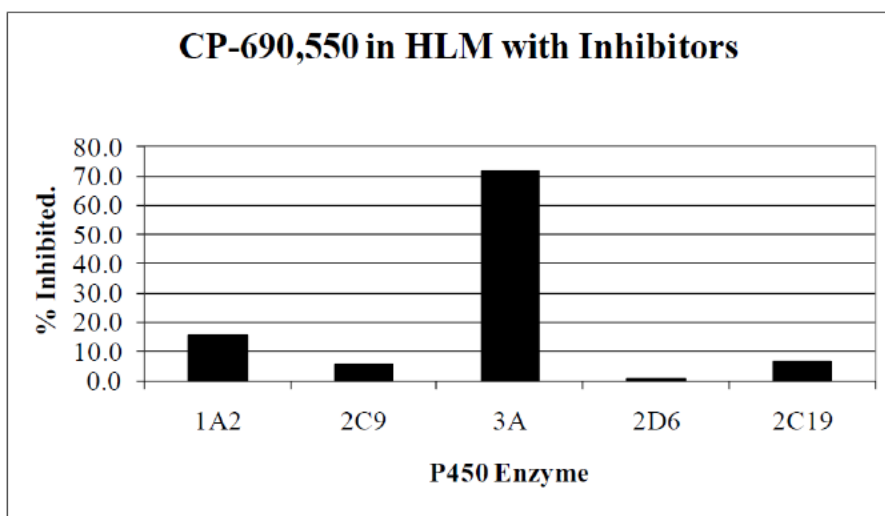


Figure 52: Percent inhibition of CP-690,550 (10 μ M) human liver microsomal metabolism (30 minute incubation time and 1 mg/mL protein content) using various isoform selective chemical inhibitors

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 μ M.
- **Results and Conclusion:** Percent inhibition observed at 30 μ M 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 IC_{50} Data for CP-690,550 in Human Liver Microsomes

Marker Substrate Activity	Enzyme	% of control at		IC ₅₀ (μM)	
		[I] = 30 μM		Mean	± SE
Phenacetin <i>O</i> -Deethylase	CYP1A2	100		>30	
Bupropion Hydroxylase	CYP2B6	81		>30	
Amodiaquine <i>N</i> -Deethylase	CYP2C8	95		>30	
Diclofenac 4'-Hydroxylase	CYP2C9	81		>30	
<i>S</i> -Mephenytoin 4'-Hydroxylase	CYP2C19	96		>30	
Dextromethorphan <i>O</i> -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) 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 C_{max} value for parent drug was 397 ng/mL and for total radioactivity was 611 ng-equiv/mL. $\text{AUC}_{0-\text{inf}}$ values for parent ranged from 977-2060 ng*h/mL and for total radioactivity it was 2430-4700 ng-equiv*h/mL with a mean value of 3440 ng-equiv*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

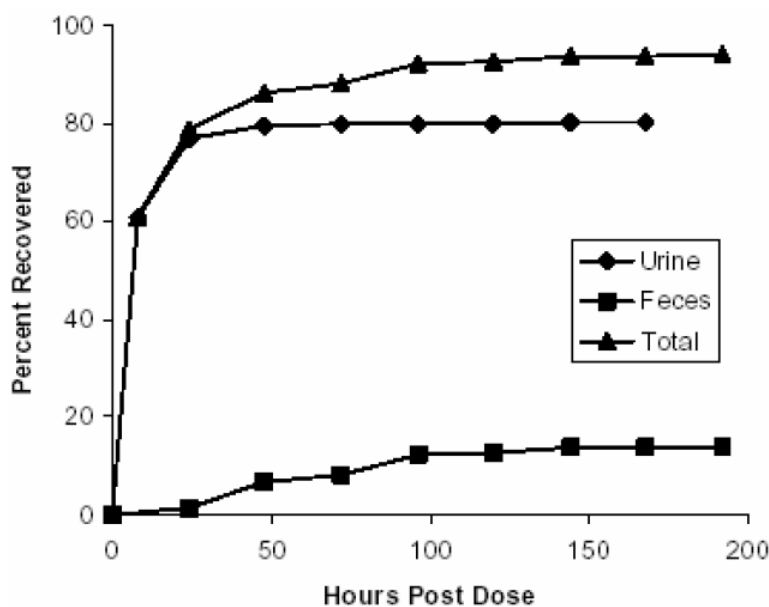


Figure 53: Cumulative Mean Recovery of Administered Radioactivity in Urine and Feces from Male Subjects over 192 Hours Following Oral Administration of a Single 50 mg Dose of [¹⁴C]CP-690,550

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 [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

Table 43: 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

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

Metabolites	m/z	Ret.Time (min)	Percent of Dose							
			Subject #						Mean	SD
			1	2	3	4	5	6		
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 [¹⁴C]CP-690,550

Metabolites	m/z	Ret.Time (min)	Percent of Dose							
			Subject #						Mean	SD
			1	2	3	4	5	6		
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-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.

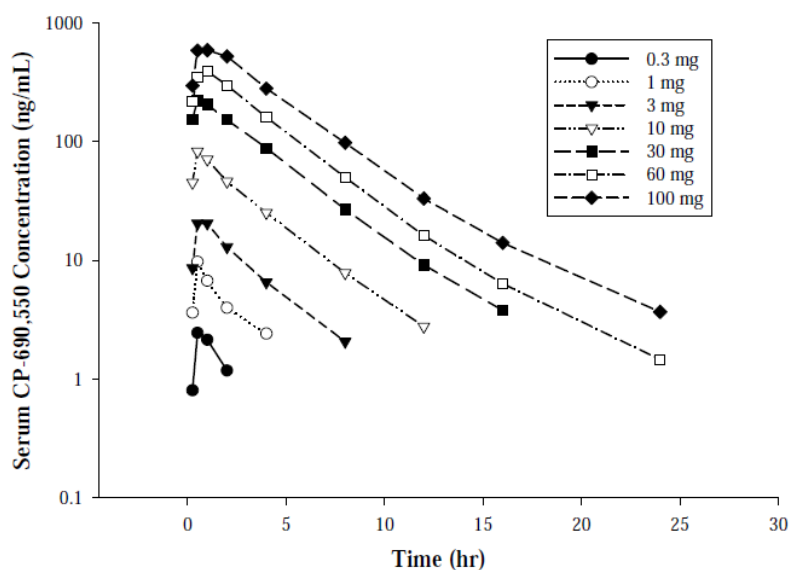


Figure 54: Mean Serum CP-690,550 Concentrations vs Times Following Administration of a Single Oral OPC Dose of CP-690,550 to Fasted Healthy Subjects

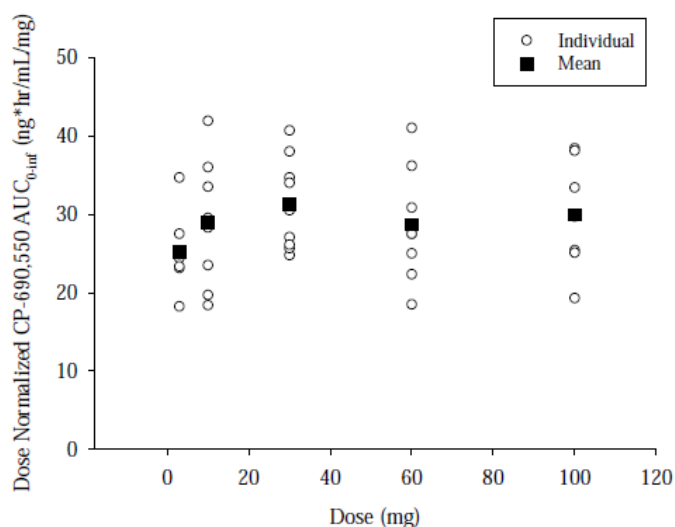


Figure 55: Dose Normalized CP-690,550 AUC_{0-inf} Following Administration of a Single Oral OPC Dose (3 to 100 mg) of CP-690,550 to Fasted Healthy Subjects

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-Tlast} (ng*hr/mL)	AUC _{0-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%.

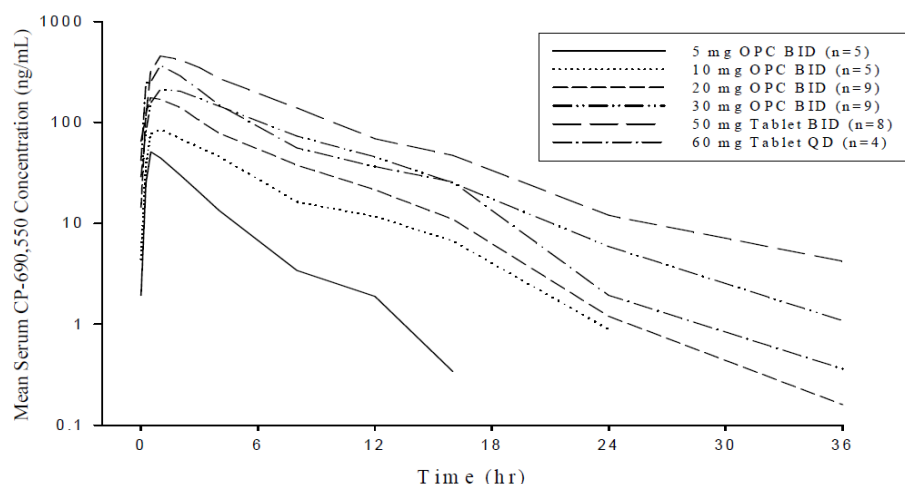


Figure 56: Mean Serum CP-690,550 Concentrations Versus Time on Day 14 Following Multiple Oral Dosing with CP-690,550 in Medically Stable Subjects with Psoriasis

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-τ} ng h/mL		R _{ac}	T _{max} h ^a		t _{1/2} hr
	Day 1	Day 14	Day 1	Day 14		Day 1	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 t_{max}

^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-tau}; CL_R = renal clearance; CL_R / Fu = renal clearance of unbound drug, where Fu was determined from in vitro human protein binding data³.

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 (CL_{cr}) 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 guidance⁴ in terms of CL_{cr}

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

cut-offs. FDA's guidance indicate CL_{Cr} ≥ 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 CL_{Cr} 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/m²). 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 C_{max} (90% CI) for these cases were respectively: 1% (-31%, 49%), 2% (-31%, 52%), and 21% (-19%, 81%).
- On continuous scale of CL_{Cr}, there was an increase in AUC_{inf} with decline in renal function (Figure 57)
- Measured unbound renal clearance for almost all subjects was greater than the individual estimated CL_{Cr} (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.

<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

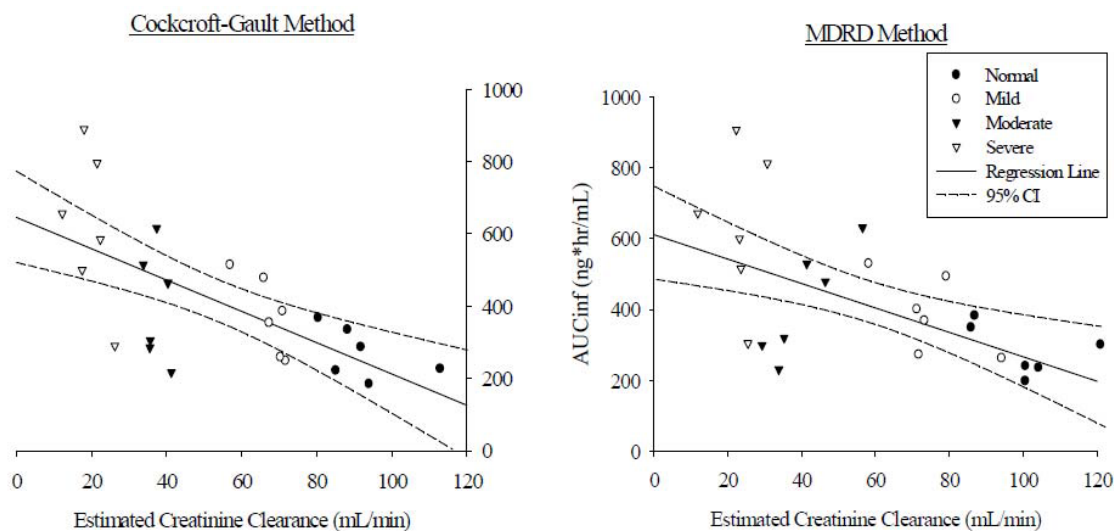


Figure 57: Individual AUC_{0-inf} vs. estimated creatinine clearances following a single 10 mg dose of CP-690,550 in subjects with normal renal function, and in subjects with mild, moderate, and severe renal impairment (Sponsor reported).

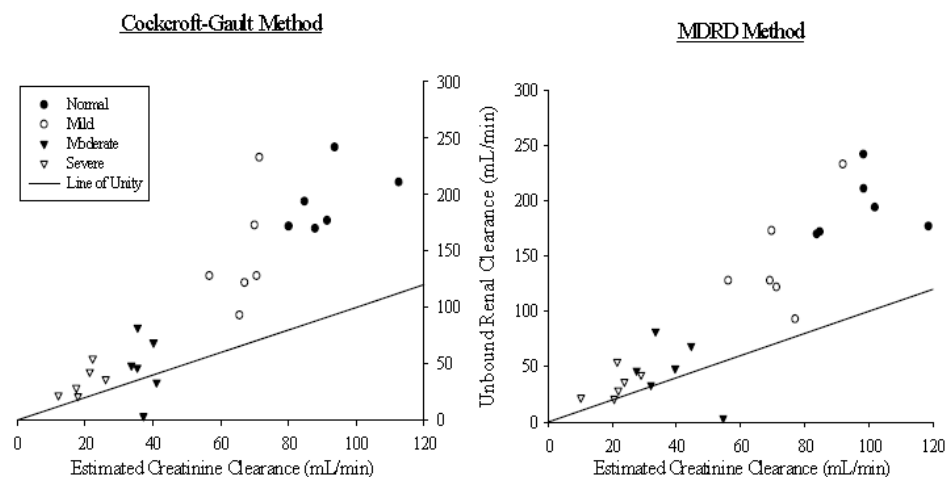


Figure 58: Individual CP-690,550 Unbound Renal Clearance (CLR/Fu) Levels Versus Estimated Creatinine Clearances Following A Single 10 mg Oral Dose of CP 690,550 in

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).

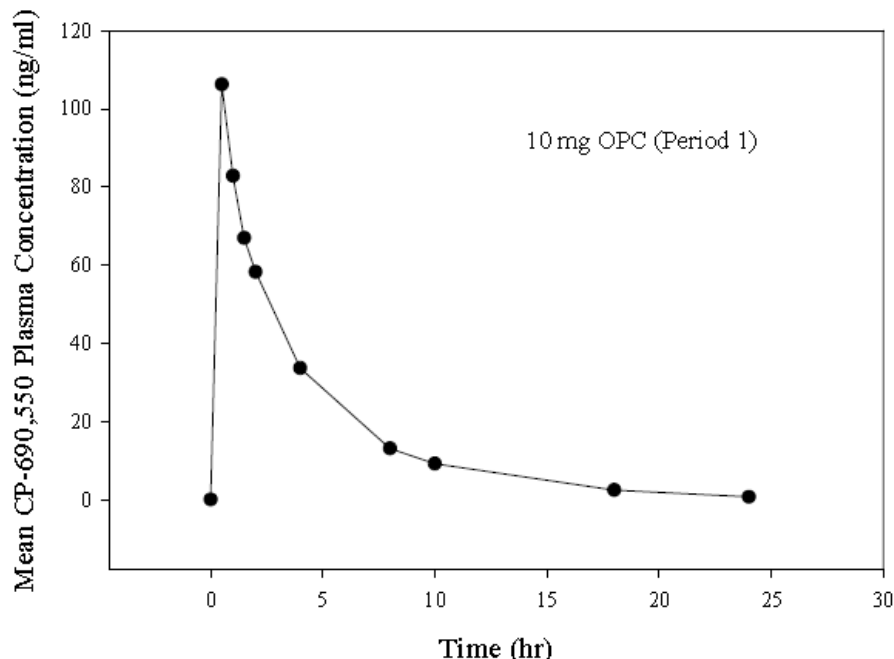


Figure 59: Mean Plasma CP-690,550 Concentrations Over Time Following administration of single dose of 10 mg CP-690,550 in end stage renal disease patients (period 1)

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	396	106	0.5	3.46	501
(SD)	(158)	(23.9)	(0.5 – 0.5)	(1.18)	(243)

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

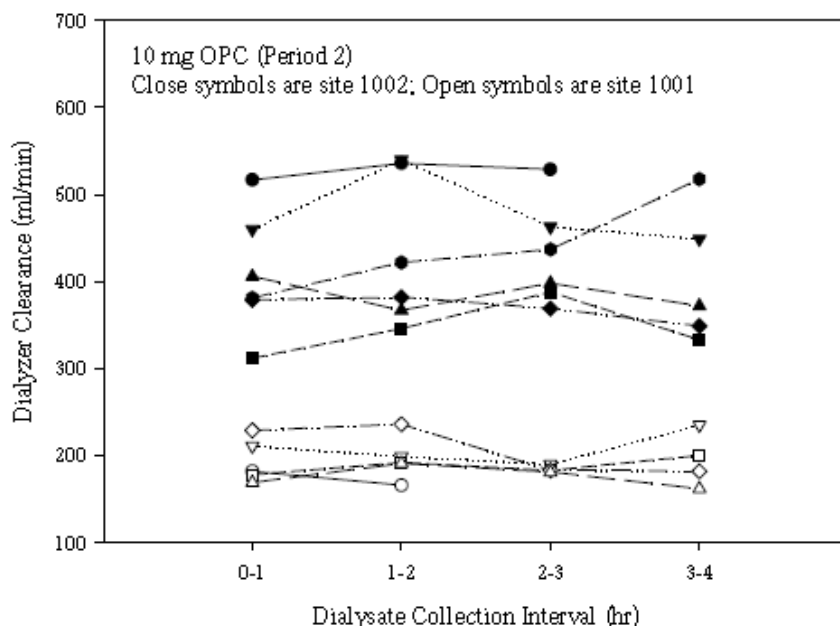


Figure 60: Individual Dialyzer Clearance of CP-690,550 over Dialysate Collection Intervals Following Administration of a Single Dose of 10 mg CP-690,550 OPC 4 Hours Prior to hemodialysis in subjects with ESRD (Period 2)

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

	CL _{HD} (mL/min)	Q _b (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 (CL_r) of PAH was calculated as:

$$= \text{UPAH} \cdot V / \text{PPAH}$$
 (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}

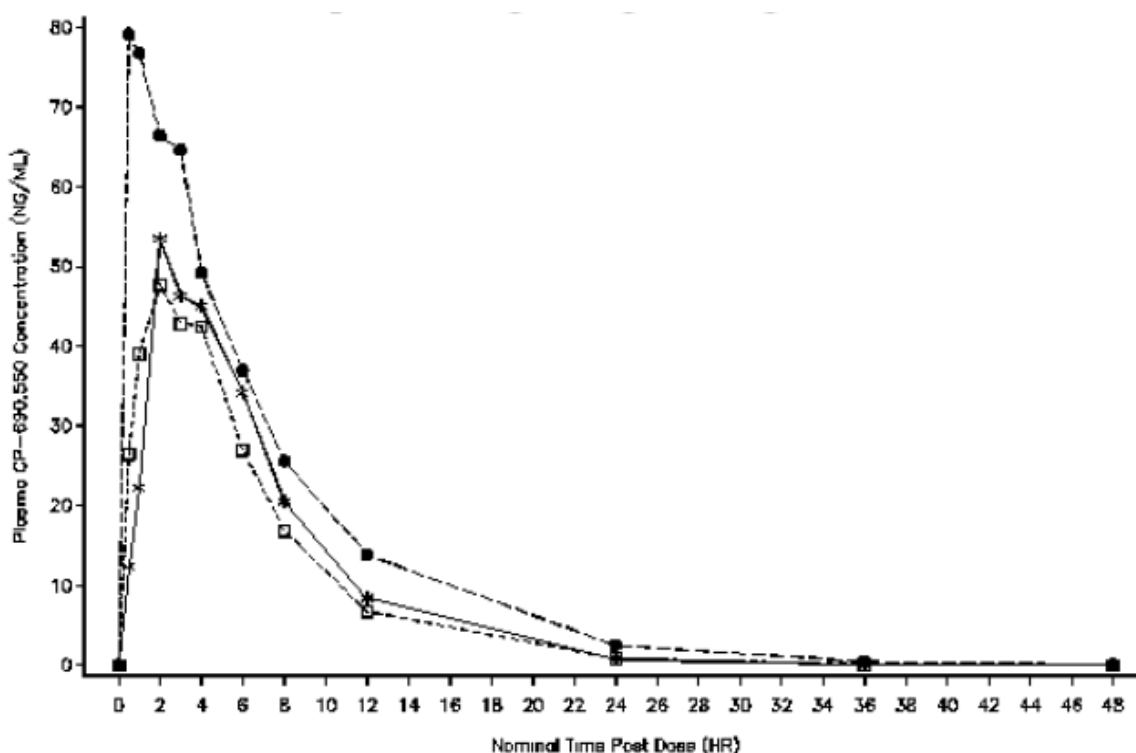
Table 55). Subjects with moderate hepatic impairment had 65% increase in AUC and 49% increase in C_{max} (Table 55).

• **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.



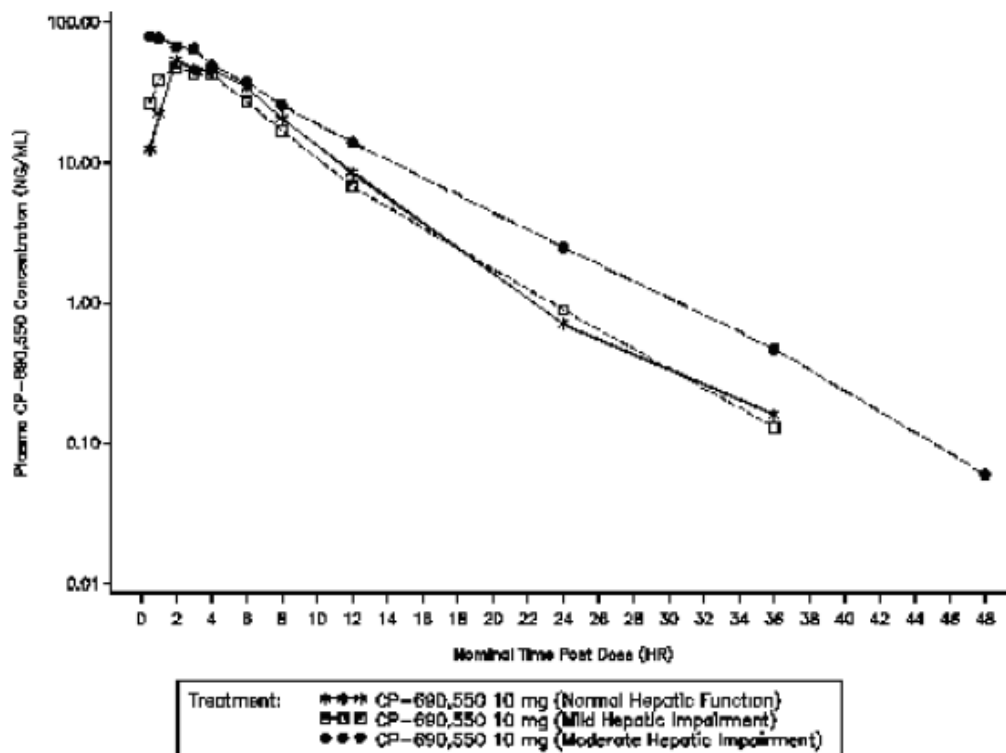


Figure 61: Median Plasma CP-690,550 Concentration-Time Profiles by Hepatic function group following a single 10 mg oral dose

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)
t _{1/2} (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, t_{1/2} = 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 t_{1/2}.

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 intestine⁵. Moreover, since single-dose of ketoconazole is likely to maintain more than 50% inhibition of intrinsic clearance of both organs for up to 10 hours², 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**

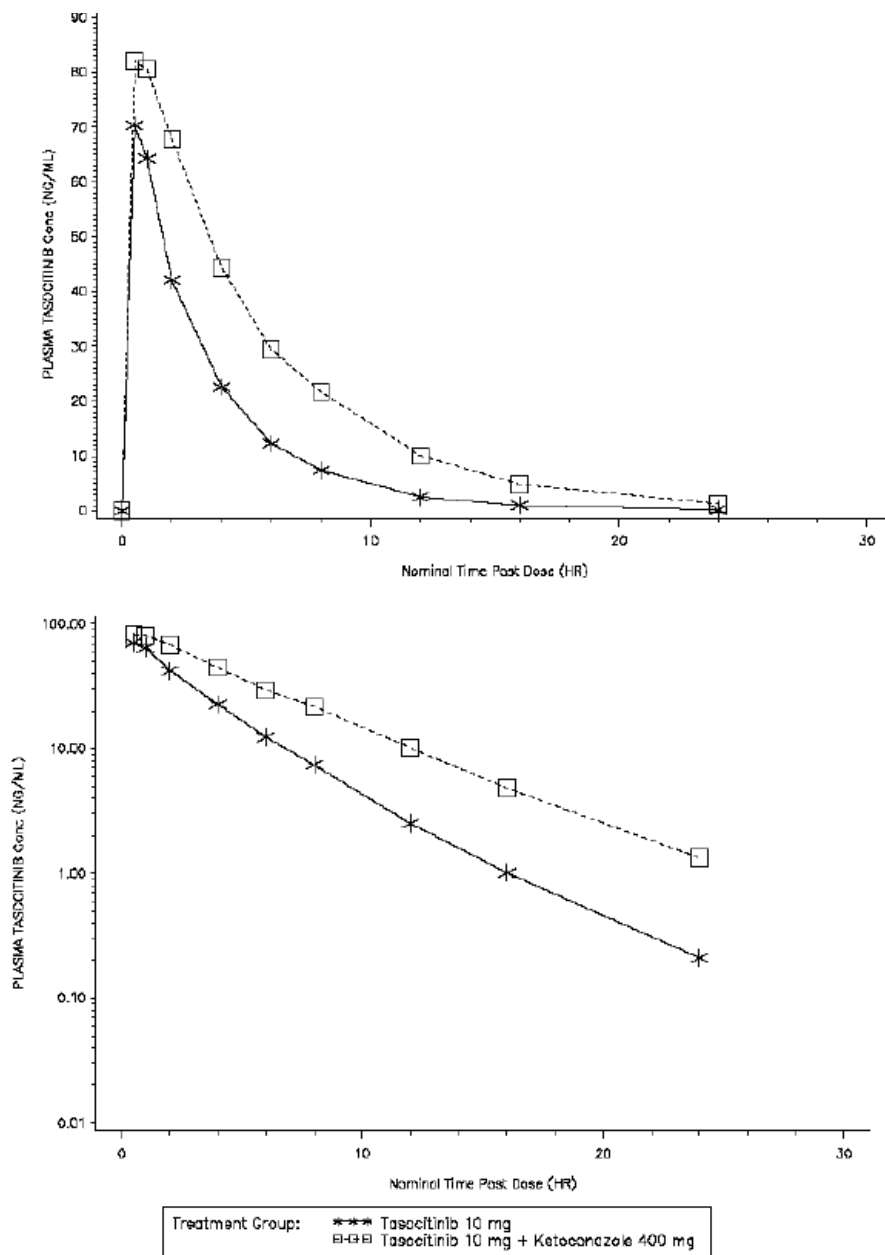


Figure 62: Median plasma CP-690,550 concentration-time profiles following single oral 10 mg dose alone and with multiple-dose ketoconazole

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

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means ^a	90% CI for Ratio
	Test (CP-690,550 10 mg + Ketoconazole 400 mg)	Reference (CP-690,550 10 mg)		
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)
	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	

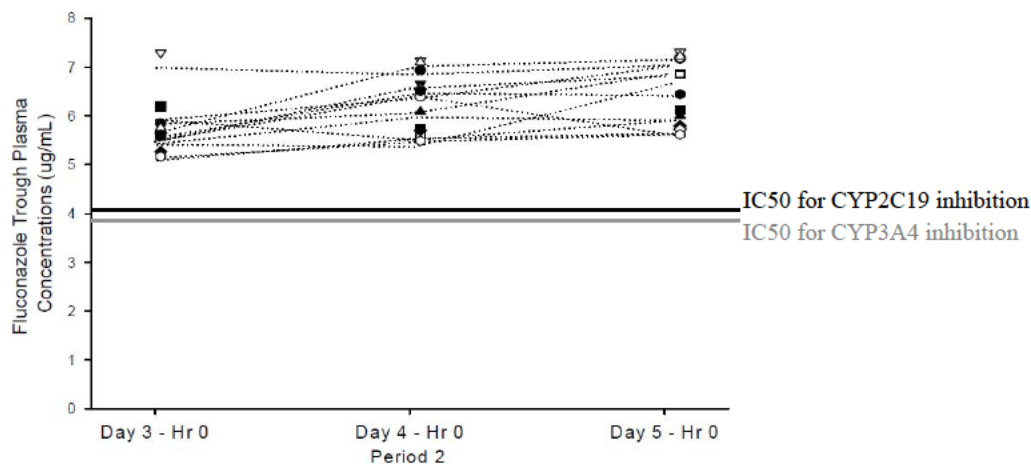
*Note: Day is relative to the first day of dosing for each period.

QC = once daily

Reviewer's comment:

Fluconazole is a moderately potent inhibitor of CYP3A4 and a strong inhibitor of CYP2C19⁶ 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 therapy⁷. 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 ($>5 \mu\text{g/mL}$, see Figure 63) were higher than the IC_{50} values for CYP3A4 (i.e., $12.3 \mu\text{M}$ or $3.84 \mu\text{g/mL}$) and CYP2C19 (i.e., $13.1 \mu\text{M}$ or $4.1 \mu\text{g/mL}$) inhibition⁸, 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/2011/019949s055,019950s059,020090s0381bl.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.

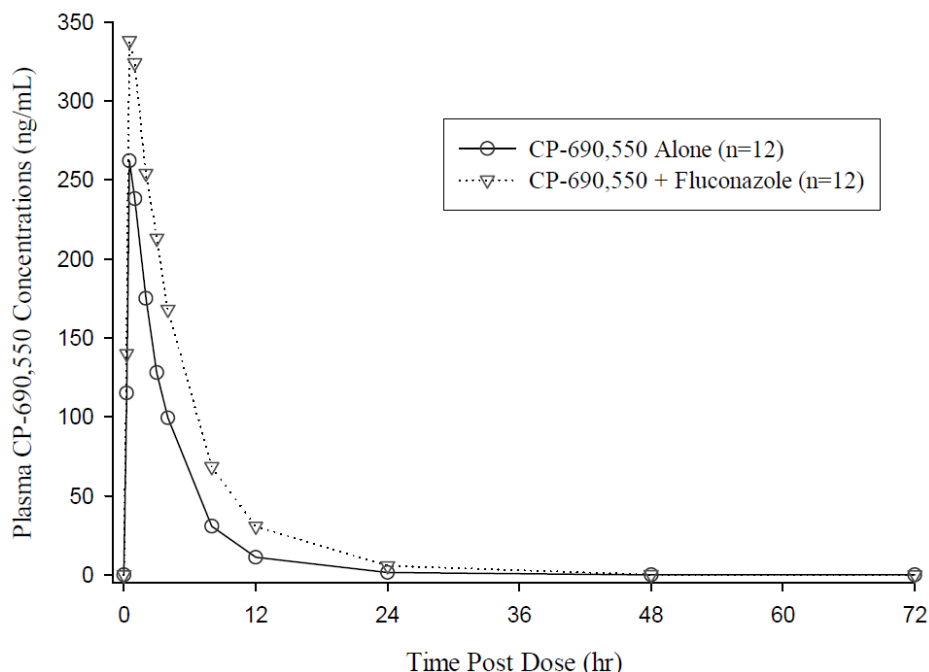


Figure 64: Plasma concentration -time profiles for CP-690,550 following a single 30 mg dose of CP-690,550 alone or in combination with fluconazole (fluconazole at steady-state)

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.

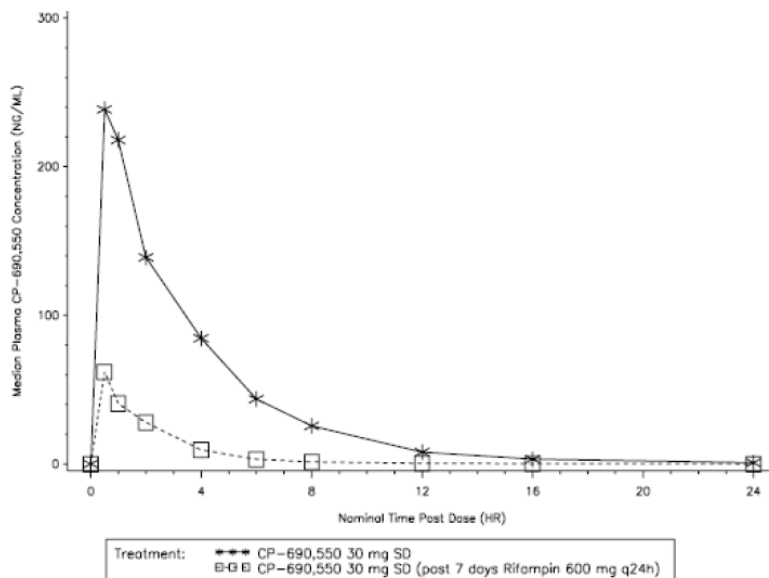


Figure 65: Median CP-690,550 Plasma Concentration-Time Profiles Following administration of CP-690,550 alone or post 7 days of rifampin 600 mg QD

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.

^aThe 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

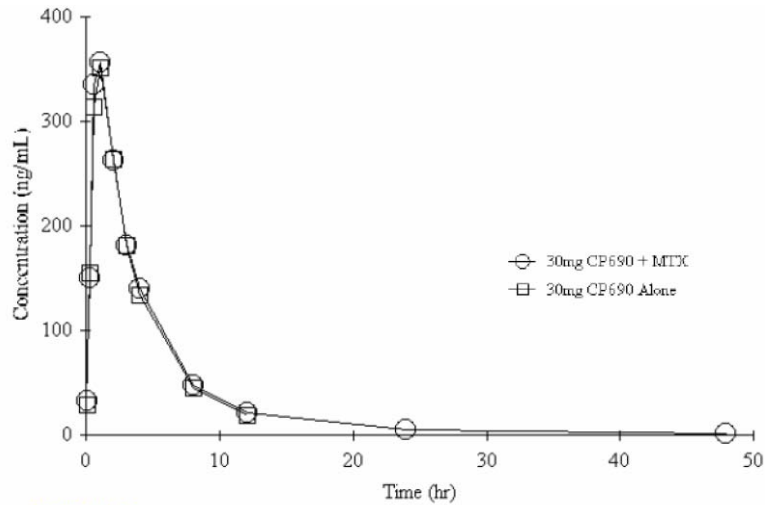
For CP-690,550 - Plasma – day 6 – up to 12 hrs and day 7 – up to 48 hrs

- **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, C_{max}) as well as amount of unchanged drug excreted in urine (Ae₁₂) 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 (Ae₂₄ and CL_R) with 23% lower Ae₂₄ 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:**

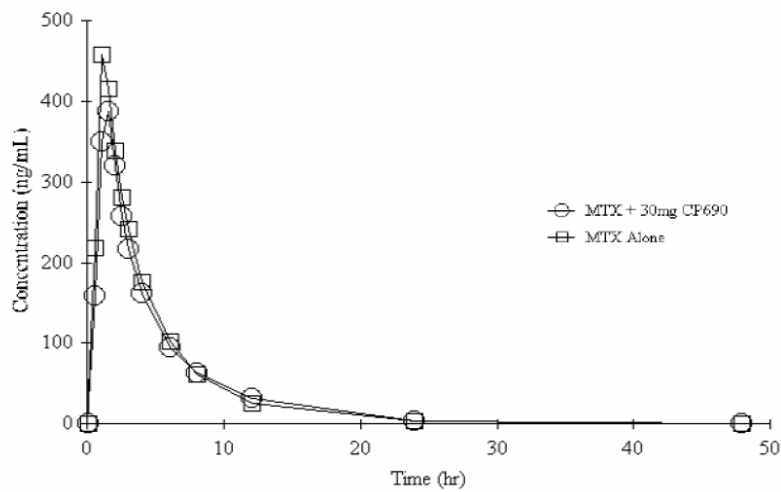
No dose adjustment recommended when CP-690,550 is coadministered with methotrexate and vice-versa no changes in methotrexate dosing are recommended following coadministration with CP-690,550.



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		0.21	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; AUC₀₋₁₂ = area under the concentration time curve from 0 to 12 hours postdose; C_{max} = maximum serum concentration;

CL/F = oral clearance; Ae₁₂ = 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		0.23	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; AUC₂₄ = area under the concentration time curve from 0 to 24 hours postdose;

C_{max} = maximum serum concentration; CL/F = oral clearance; Ae₂₄ = 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 tofacitinib and Tac and tofacitinib and CsA, because all of these drugs are immunosuppressants. 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		

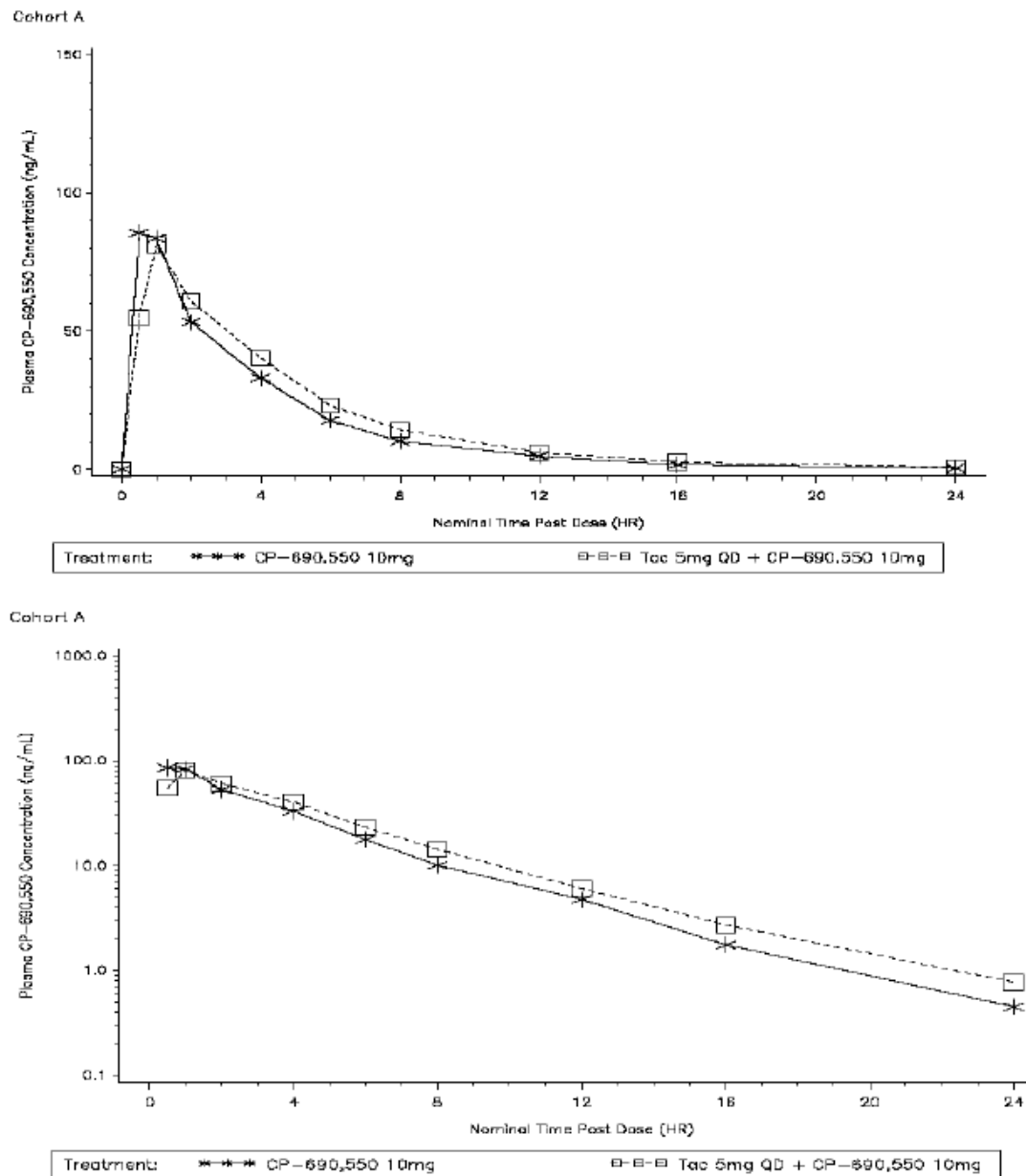
Source: [Appendix A1](#)

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.

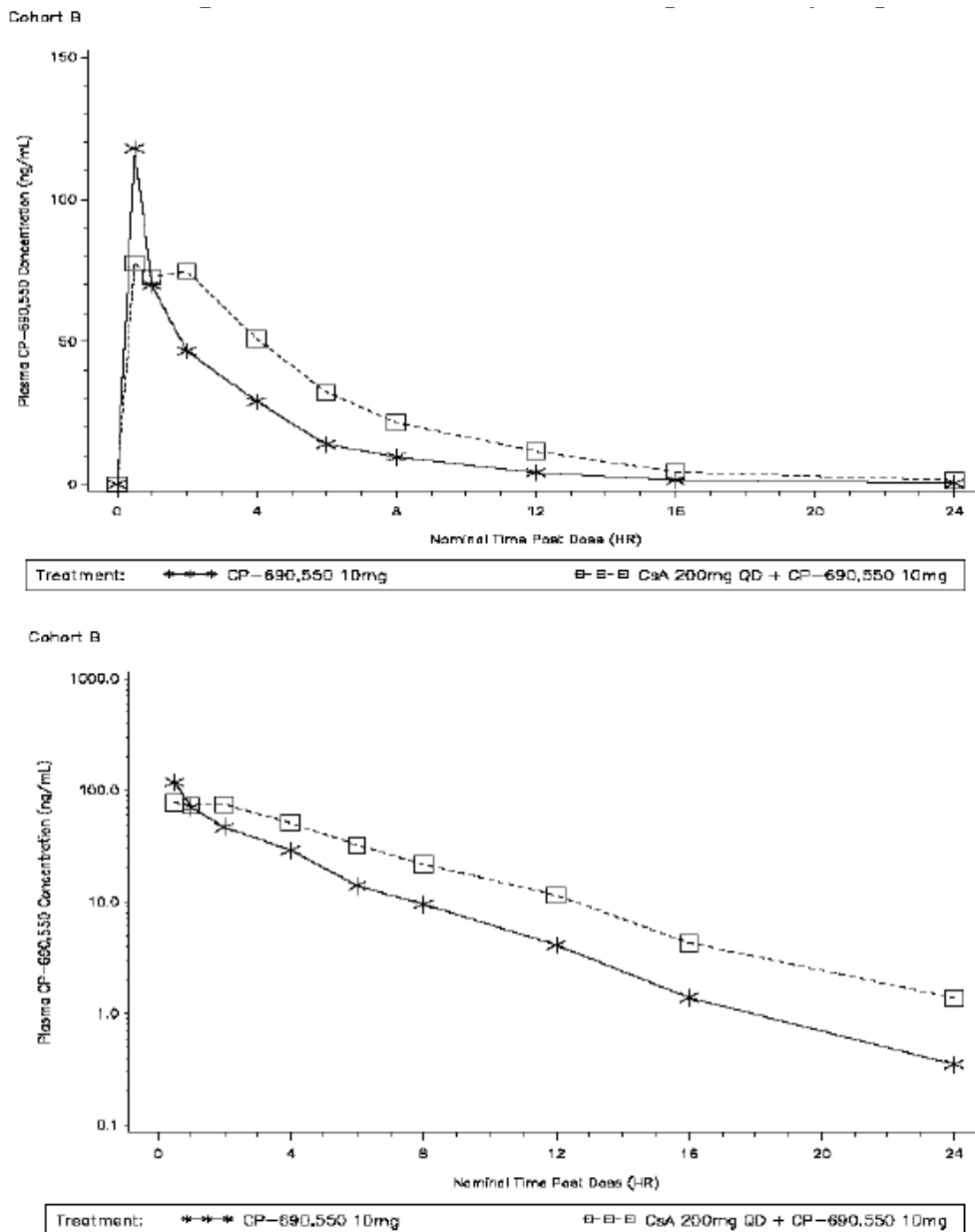


Source: Figures 14.1.1.1 and 14.1.1.2

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

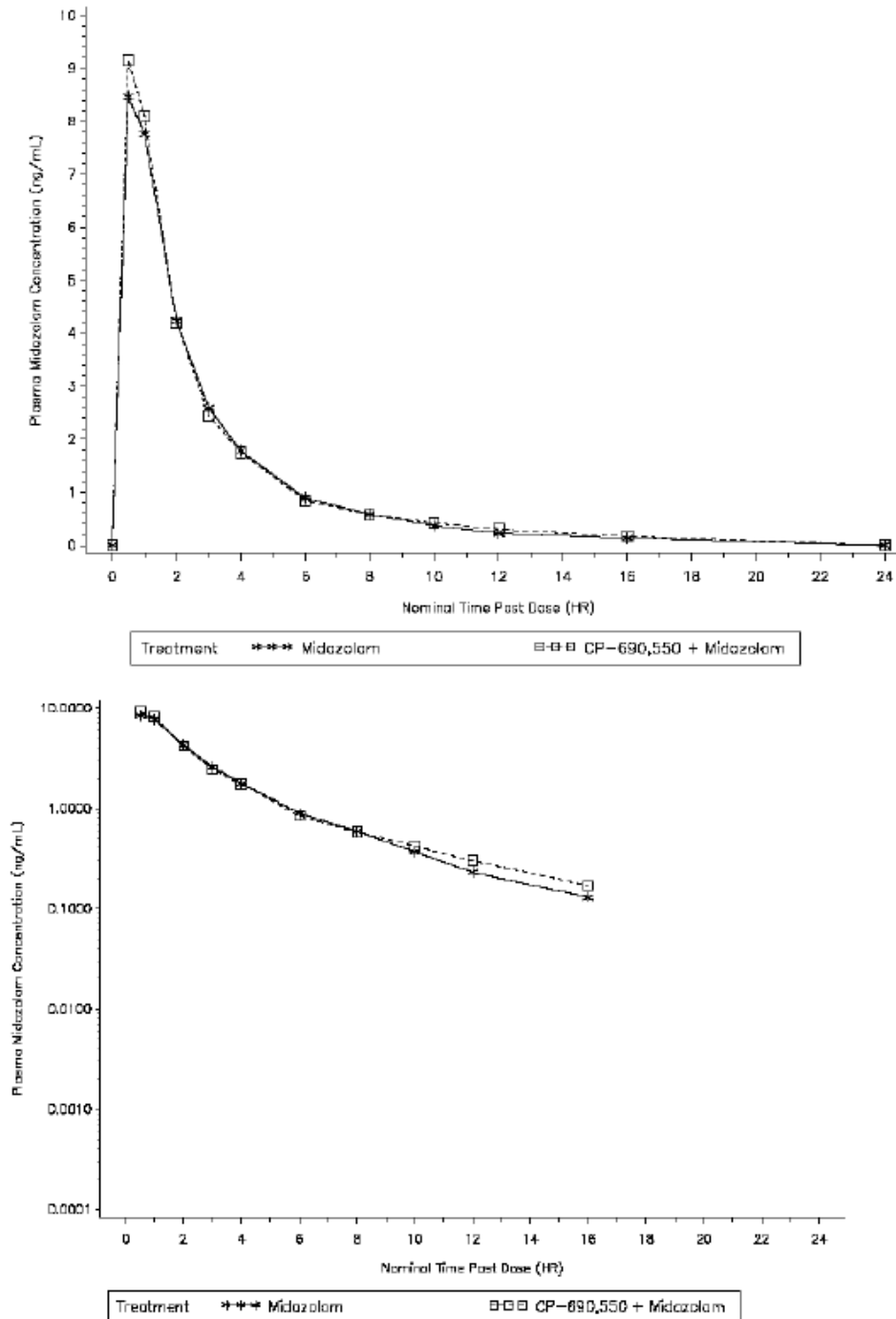
Treatment A = single administration of midazolam 2 mg oral syrup. Treatment B = administration of 30 mg CP-690,550 PO BID for 6 days, followed by administration of a concurrent, single dose of midazolam 2 mg oral syrup on the morning of Day 7. Dosing with 30 mg CP-690,550 PO BID continued through the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

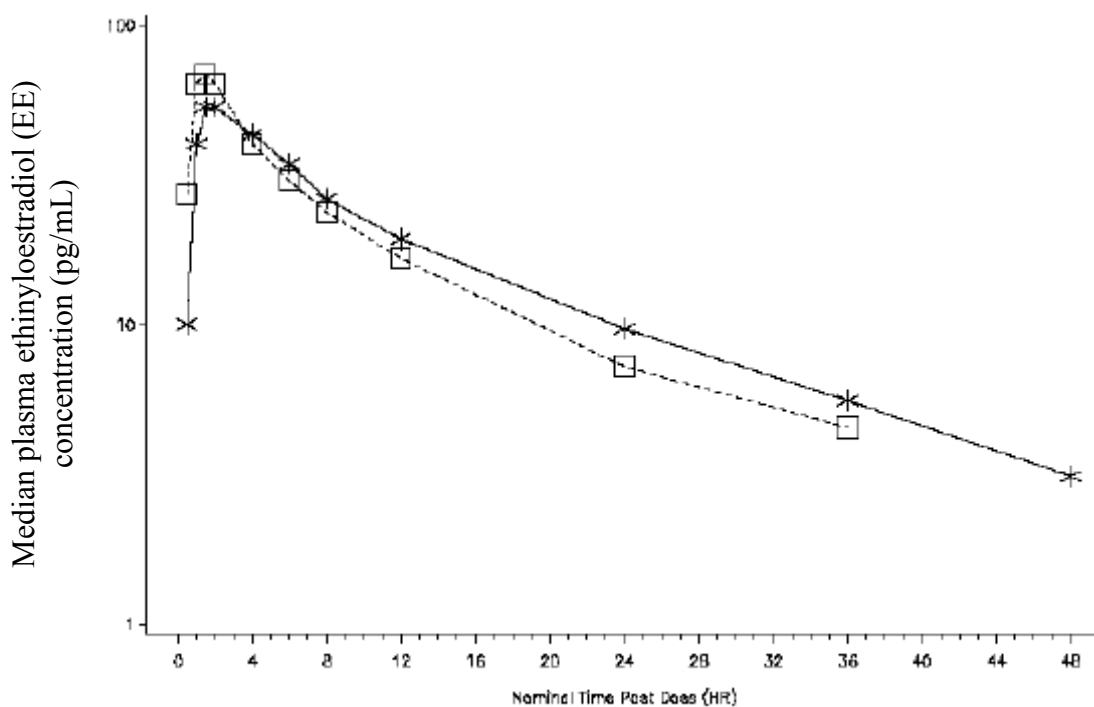
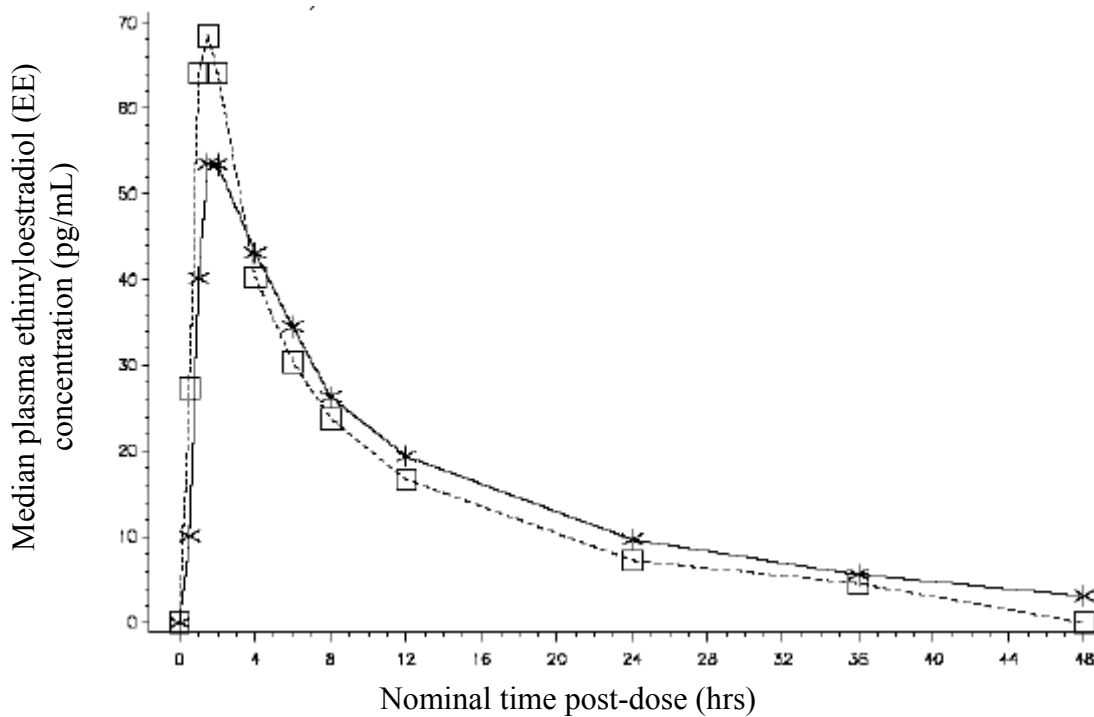


Figure 71: Median plasma ethinyloestradiol concentration - time profiles following single oral microgynon 30 dose alone and with multiple dose CP-690,550

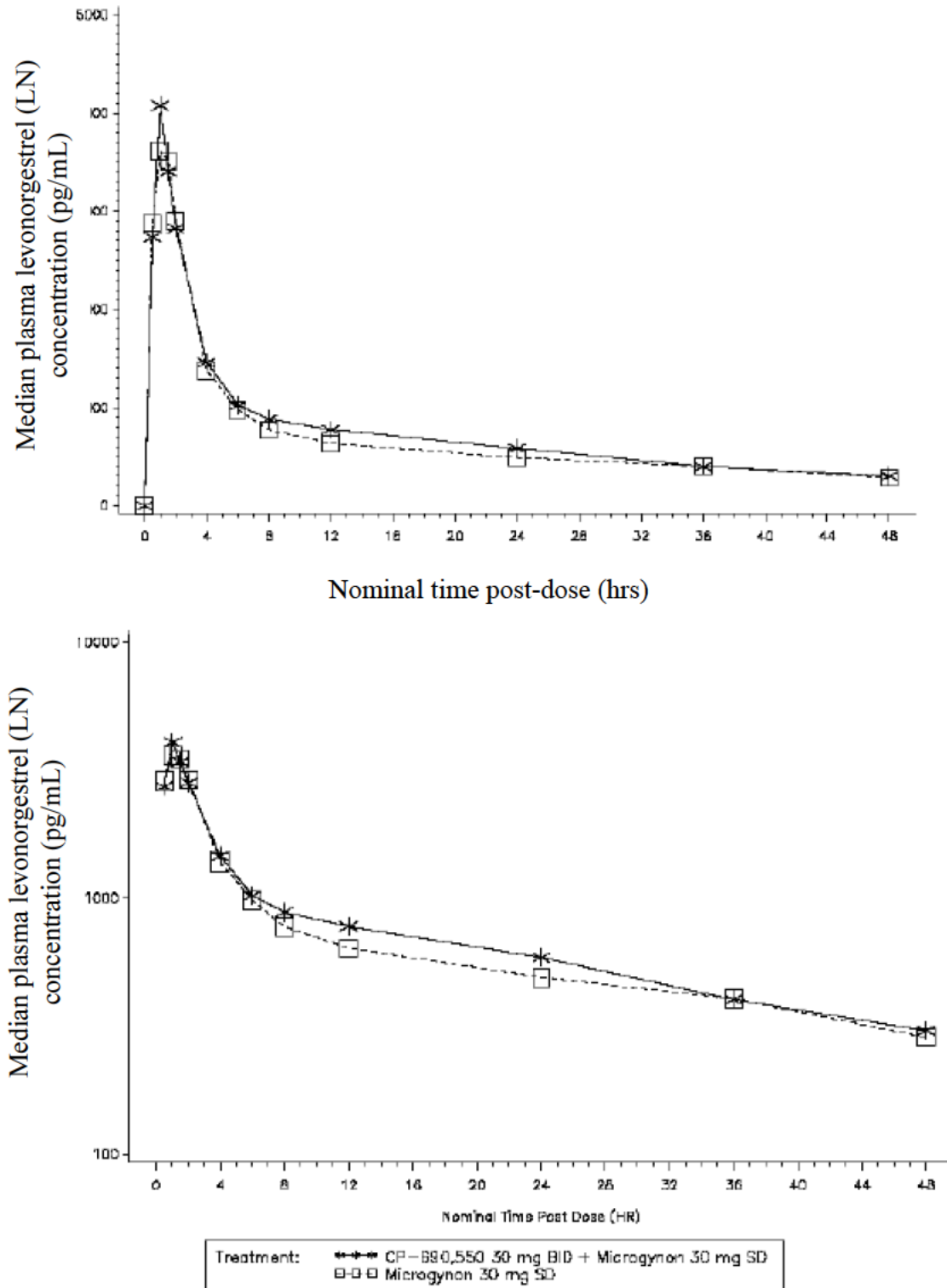


Figure 72: Median plasma levonorgestrel concentration - time profiles following single oral microgynon 30 dose alone and with multiple dose CP-690,550

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

Ethinylloestradiol Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means ^a	90% CI for Ratio
	Microgynon 30 With CP-690,550 (Test)	Microgynon 30 Alone (Reference)		
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		Ratio (Test/Reference) of Adjusted Geometric Means ^a	90% CI for Ratio
	Microgynon 30 With CP-690,550 (Test)	Microgynon 30 Alone (Reference)		
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		Ratio (Test/Reference) of Adjusted Geometric Means ^a	90% CI for Ratio
	10 mg Oral Tablet (Test)	10 mg IV Infusion (Reference)		
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 _{inf} (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

Parameter	Arithmetic Mean (SD)		Adjusted Geometric Mean ^b		Comparison	
	Tablet - Fasting	OPC - Fasting	Tablet - Fasting	OPC - Fasting	Ratio (%)	95% CI (%)
	Test	Reference	Test	Reference	T/R	Lower, Upper
AUC _{0-∞} (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

Parameter	Arithmetic Mean (SD)		Adjusted Geometric Mean ^b		Comparison	
	Tablet - Fed	Tablet - Fasting	Tablet - Fed	Tablet - Fasting	Ratio (%)	95% CI (%)
	Test	Reference	Test	Reference	T/R	Lower, Upper
AUC _{0-∞} (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 _{1/2} (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_{1/2}.

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

Pharmacokinetic Parameter, Units	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means ^a	90% CI for Ratio
	Test (CP-690,550 10 mg Fed SD)	Reference (CP-690,550 10 mg Fasted SD)		
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

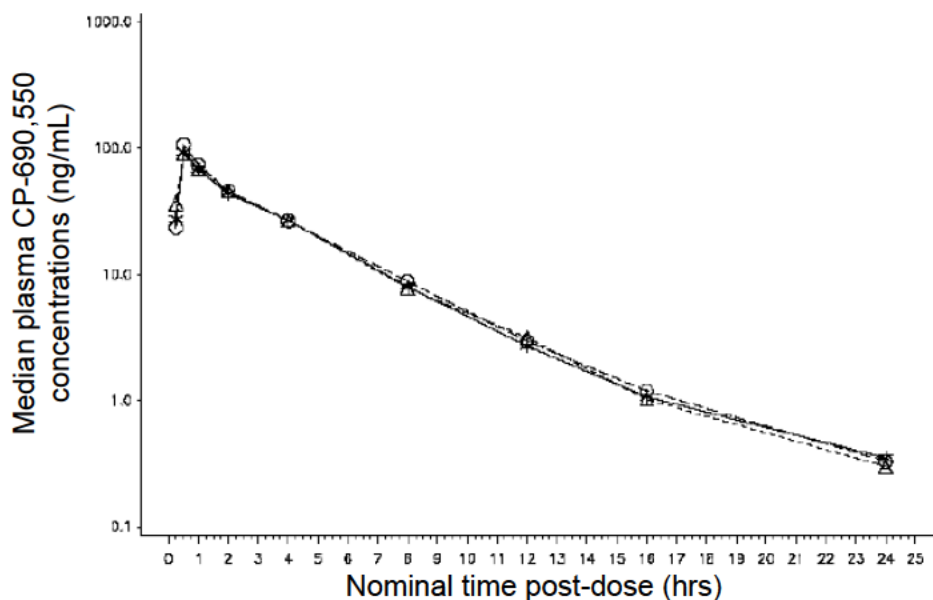
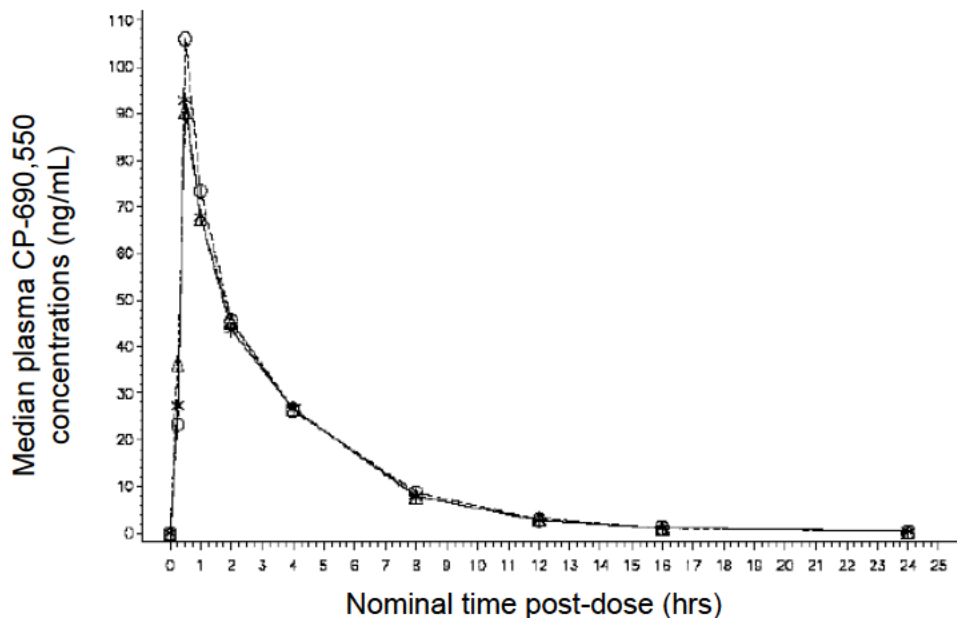
• Results

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		Ratio (Test/Reference) of Adjusted Geometric Means ^a	90% CI for Ratio
	Test	Reference		
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).

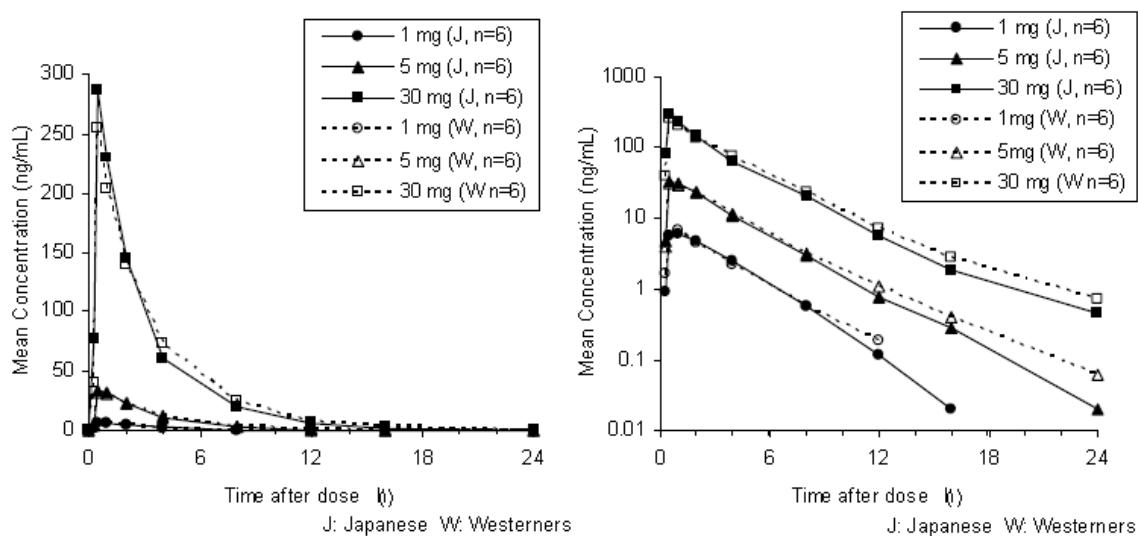


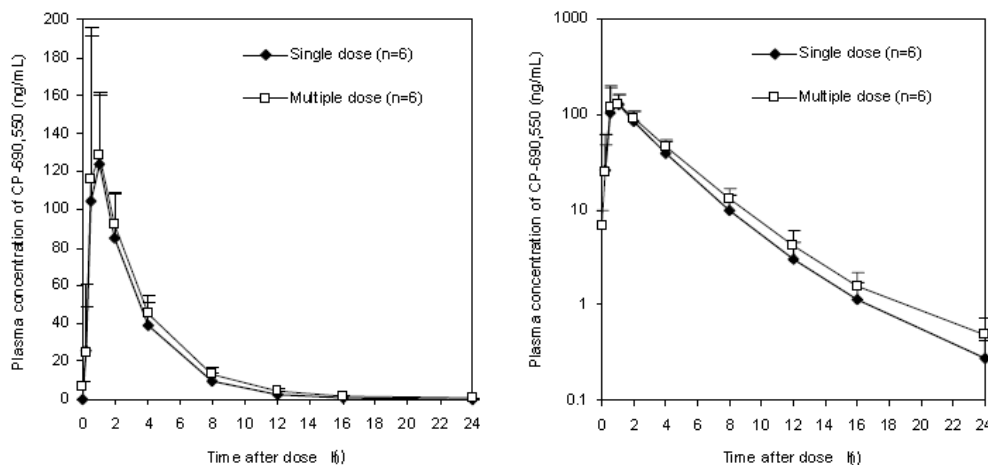
Figure 74: Mean plasma concentration of CP-690,550 following single oral dose administration in healthy Japanese and Western subjects

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
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_{1/2} (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 single 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: 161.1

- **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

CP-690,550 Parameter (Units)	Summary Statistics ^a by Treatment	
	Day 1 (Single-Dose)	Day 6 (Multiple-Dose)
N	12	12
AUC ₀₋₁₂ (ng·hr/mL)	274.8 (13)	NA
AUC ₀₋₂₄ (ng·hr/mL)	273.8 (13)	NA
AUC _{0-∞} (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 _{ough} (ng/mL)	NA	4.688 (38)
t _{1/2} (hr)	3.319 (12)	2.479 (11)
R _{ss}	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_{1/2}.

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/s/

LOKESH JAIN
06/22/2012

VENKATESH A BHATTARAM
06/23/2012

JEFFREY B KRAFT
06/25/2012

MICHAEL A PACANOWSKI
06/25/2012

SURESH DODDAPANENI
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:

- 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).
- The Applicant's proposal of using the disintegration test in lieu of the dissolution test is acceptable.
- (b) (4) The Applicant already agreed to keep the disintegration test in the drug product's specifications table for release and stability.
- 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.

Reviewer

ONDQA Biopharmaceutics

Date

Angelica Dorantes, Ph.D.

ONDQA Biopharmaceutics Team Leader

Date

cc: NDA 203-214 *Darrrts*

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.



Batch-Strength-Container-Condition

Disintegration Time for Stability Batches after 3 Months

(b) (4)



Batch-Strength-Container-Condition

Disintegration Time for Stability Batches after 6 Months

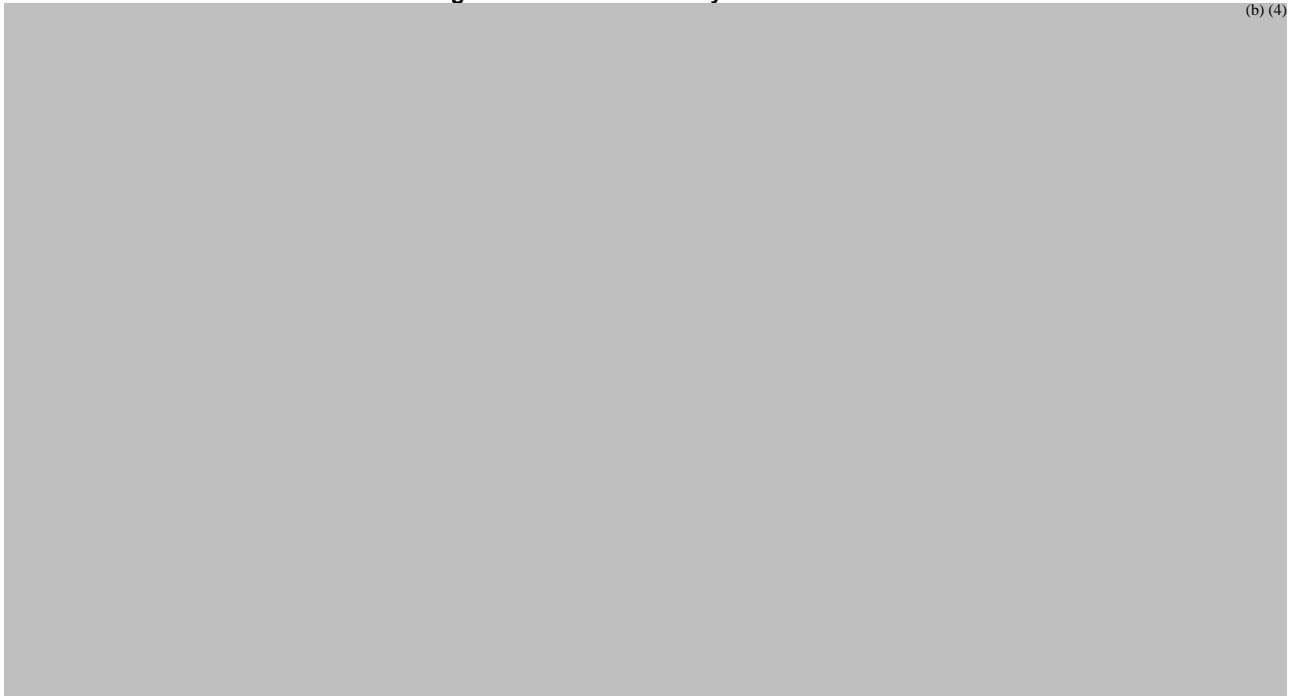
(b) (4)



Batch-Strength-Container-Condition

Disintegration Time for Stability Batches after 9 Months

(b) (4)



Batch-Strength-Container-Condition

(b) (4)



Batch-Strength-Container-Condition

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 JK1 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	ID (LC)	Retention time of the main peak matches that of reference standard
Identity	Positive for active ingredient	ID (NIR/UV and LC)	NIR: Positive identification UV & LC: Spectrum of the major peak matches that of the reference standard
		Assay (NIR/LC)	95.0-105.0% of Label Claim - EU 90.0-110.0% of Label Claim - US
Strength	5 mg and 10 mg	Specified Degradants (LC)	(b) (4)
Assay	Meet pharmacopeia requirements	Unspecified Degradants (LC):	
Degradants and Impurities	Meets criteria of ICH Q3B(R2)	Total Degradation (LC)	
		Uniformity of Dosage Units (NIR/LC)	Meets pharmacopeia requirements
Uniformity of Dose	Meets pharmacopeia requirements	Disintegration	Within (b) (4)
Drug Release	Rapid disintegration and dissolution	Microbiological limits	Meets pharmacopeia requirements
Microbiological Limits	Meets pharmacopeia requirements	Excipient CoA	Meets pharmacopeia requirements
Intended Markets	US, EU, Japan, and others	Registration Stability Testing	Meets specifications at the end of shelf life (b) (4)
Formulation Ingredients	Acceptable for intended markets		
Shelf Life	Minimum 24 months	CoA Provided by Supplier	Conforms
Packaging Materials	(b) (4) sealed HDPE bottle with desiccant	Package Check	Conforms
Primary Packaging	(b) (4) bottles		

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	(b) (4)
Lactose Monohydrate		NF, Ph. Eur., JP	
Croscarmellose Sodium		NF, Ph. Eur., JP	
Magnesium Stearate		NF, Ph. Eur., JP	
(b) (4)		Pfizer	
Total Finished Tablet ⁵		USP, Ph. Eur., JP	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 (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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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.

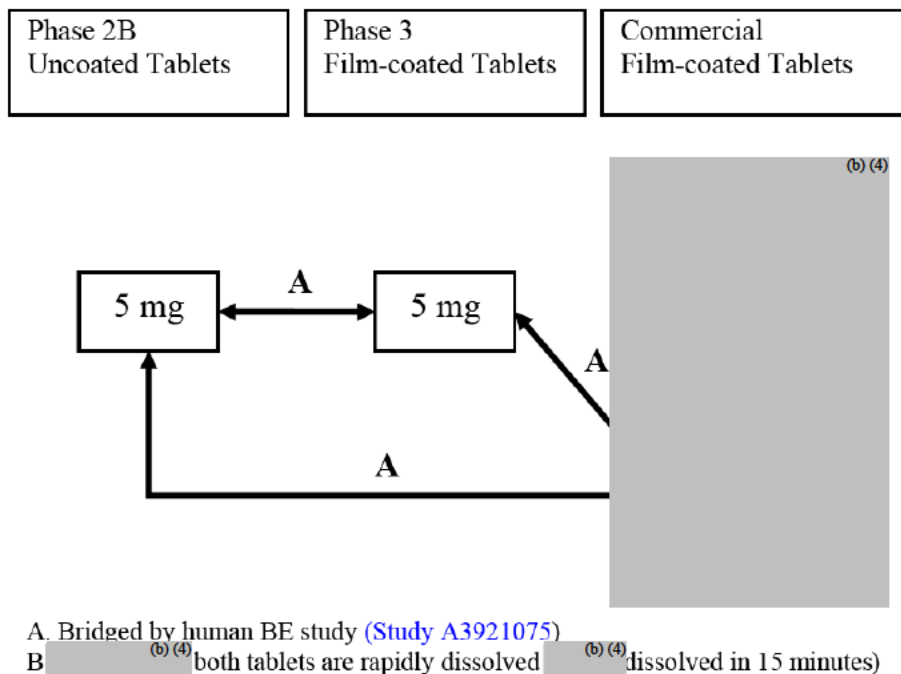
n = number of subjects in subgroup.

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



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. [REDACTED] (b) (4)
 [REDACTED]. Implement this criterion and provide a revised specification table for your drug product. [REDACTED] (b) (4)

At the present time, in accordance with CFR, the disintegration test is required. However, if an acceptable alternate measure of bioavailability is provided, the [REDACTED] (b) (4)

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.

[REDACTED] (b) (4)

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.

[REDACTED] (b) (4)
 [REDACTED] Based on the information you provided, the disintegration time is less than [REDACTED] (b) (4) 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.

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/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				
Genotype/phenotype studies	X	1		Thorough QTc study 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, ACR70, 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.

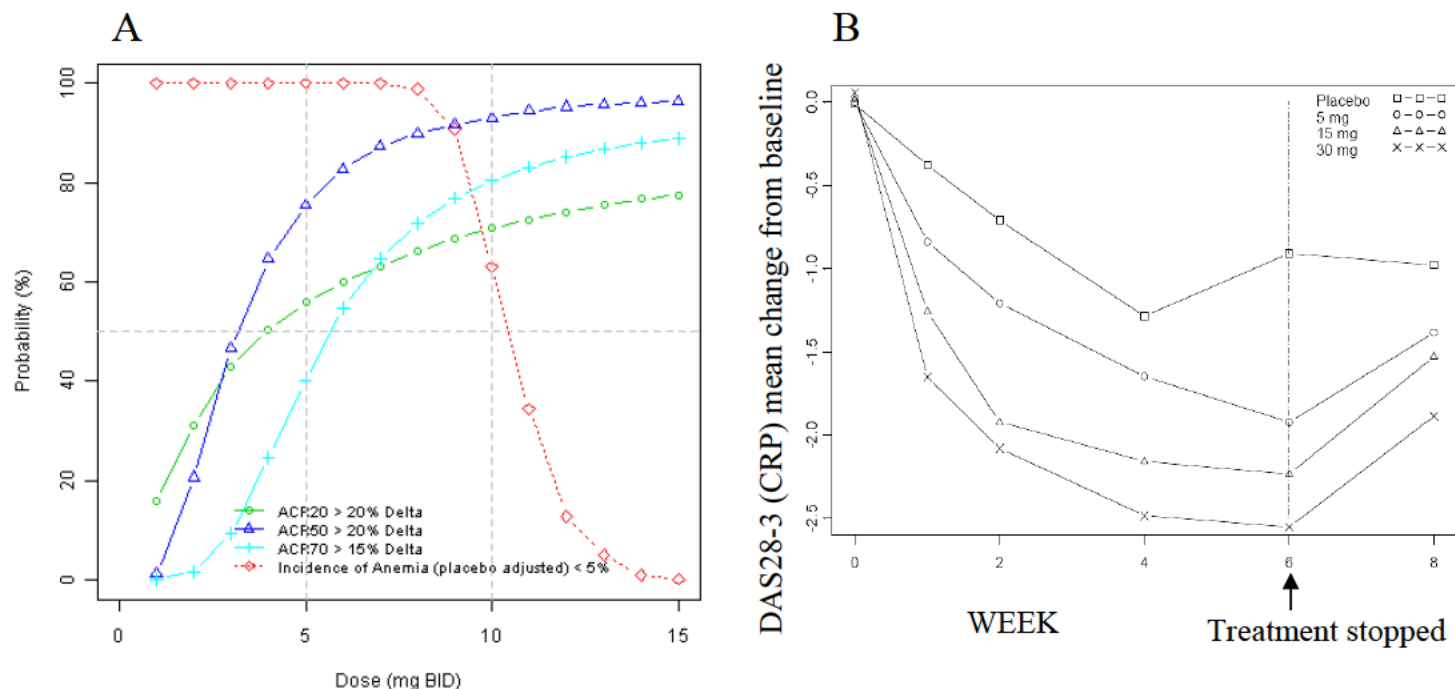


Figure 1. (A) Probability of achieving target effects for efficacy (ACR20, ACR50 and ACR70 response rates) and safety (anemia) endpoints based on dose response modeling of A3921025 data, and (B) DAS28-3 (CRP) mean change from baseline after 6 weeks of treatment for data from A3921019 clinical study

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**.

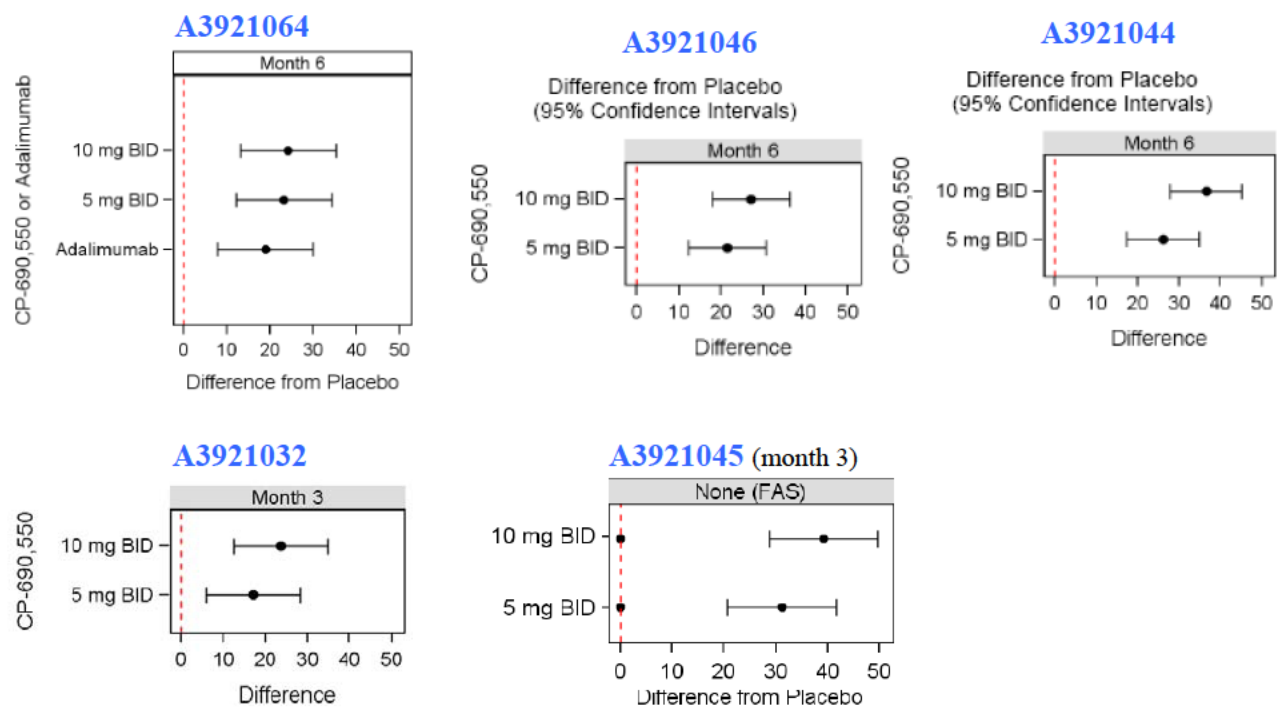


Figure 2. Placebo adjusted response rate and 90% confidence intervals for ACR20 endpoint from 5 Phase 3 trials

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.

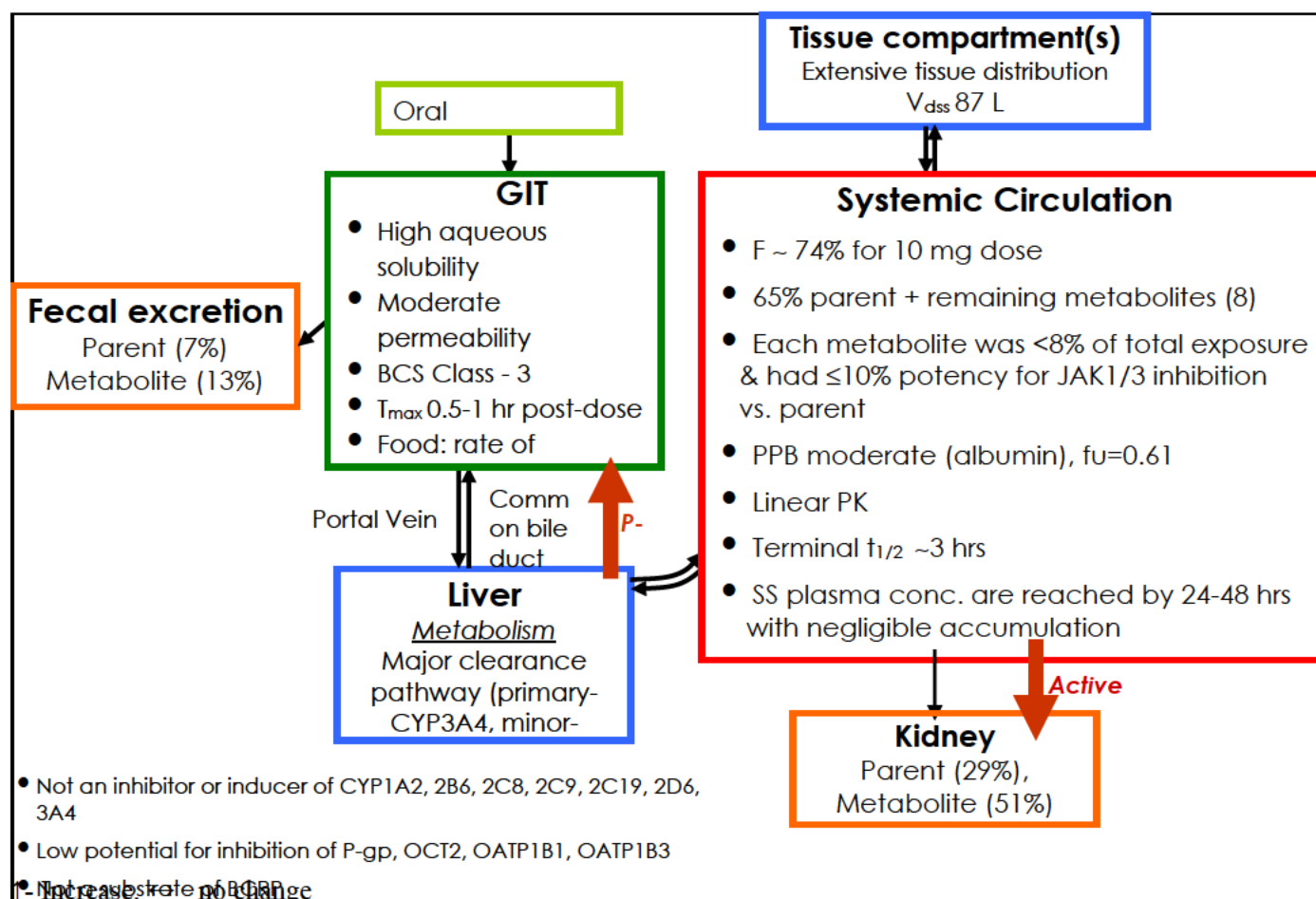


Figure 3: Schematic presentation of Tofacitinib PK properties

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
<i>Mechanism of action based PD endpoints</i>		
CRP	1-15 mg BID	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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
<i>Safety endpoints</i>		
Neutrophils	5-30 mg BID	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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 C_{max} .

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.

Mid-Cycle Deliverables

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

SURESH DODDAPANENI
12/14/2011

Exposure-response modeling using latent variables for the efficacy of a JAK3 inhibitor administered to rheumatoid arthritis patients

Matthew M. Hutmacher · Sriram Krishnaswami ·
Kenneth G. Kowalski

Received: 1 August 2007 / Accepted: 26 October 2007 / Published online: 6 December 2007
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Abstract Currently, no general methods have been developed to relate pharmacologically based models, such as indirect response models, to discrete or ordered categorical data. We propose the use of an unobservable latent variable (LV), through which indirect response models can be linked with drug exposure. The resulting indirect latent variable response model (ILVRM) is demonstrated using a case study of a JAK3 inhibitor, which was administered to patients in a rheumatoid arthritis (RA) study. The clinical endpoint for signs and symptoms in RA is the American College of Rheumatology response criterion of 20%—a binary response variable. In this case study, four exposure-response models, which have different pharmacological interpretations, were constructed and fitted using the ILVRM method. Specifically, two indirect response models, an effect compartment model, and a model which assumes instantaneous (direct) drug action were assessed and compared for their ability to predict the response data. In general, different model interpretations can influence drug inference, such as time to drug effect onset, as well as affect extrapolations of responses to untested experimental conditions, and the underlying pharmacology that operates to generate key response features does not change because the response was measured discretely. Consideration of these model interpretations can impact future study designs and ultimately provide greater insight into drug development strategies.

M. M. Hutmacher (✉) · K. G. Kowalski
Pharmacometrics Group, Pfizer Corporation, Ann Arbor, MI, USA
e-mail: matt.hutmacher@a2pg.com

Present Address:

M. M. Hutmacher
The Ann Arbor Pharmacometrics Group, Inc, Ann Arbor, MI, USA

S. Krishnaswami
Department of Clinical Pharmacology, Pfizer Corporation, Ann Arbor, MI, USA

Keywords Indirect response models · Ordered-categorical data · Concentration-response · Dose-response · Latent variable

Introduction

Indirect response models provide a semi-mechanistic framework to address temporal delays in responses relative to drug exposure profiles [1]. These models incorporate pharmacodynamic onset and maintain pharmacologic interpretation, characteristics that provide feasible (and greater confidence in) extrapolations. However, indirect response models are developed currently for continuous data only. No general theory exists for addressing drug-induced delay in binary or ordered categorical data.

Exposure-response models have been developed previously to address hysteresis in ordered categorical data. For dental pain, an effect site model was constructed to assess short delays (hours) between exposure and response after a single dose [2]. This manuscript did not provide a general methodology to incorporate longer delays or delays due to an indirect response mechanism. Empirical models, which utilized cumulative area under the concentration curve (CAUC), were also developed for multiple dose settings [3,4]. A greater delay was observed in these studies which could be attributed potentially to an indirect mechanism. The CAUC models were able to predict the temporal shift between exposure and response and identify influential covariates. The CAUC builds over time, eventually becoming larger than the E_{50} . This time-dependent accumulation relative to the ‘potency’ accounts for the temporal delay between PK and PD. However, these models suffer from two deficiencies. These models can neither mechanistically differentiate pharmacokinetic from pharmacodynamic delays, nor predict profiles of patients that discontinue medication. Model-based designs for phase 2b/3 studies often require extrapolations to untested dose regimens and unobserved visit times, or prediction of responses after medication withdrawal for randomized withdrawal designs. Pursuing empirical or CAUC models in general is unsatisfactory for these reasons: these models provide limited pharmacologic interpretation and questionable extrapolations if used for design. Mechanistic-based models are desirable to overcome these deficiencies throughout drug development.

In this manuscript, an extension of the indirect model methodology for ordered categorical data is developed using the concept of a latent variable (LV). A LV is an underlying, unobservable continuous variable, which can be mapped into binary or ordered categorical response using a threshold. The proposed methodology is motivated here by a case study. In this case study, the methodology was used to characterize the exposure-response relationship between a drug currently in development, which inhibits the Janus kinase 3 enzyme, and a discrete clinical endpoint (American College of Rheumatology response criterion of 20% improvement—ACR20).

The targeted pathway in this case study relates to the Janus kinase 3 enzyme (JAK3), which is a key signaling molecule for the common γ -chain of the IL-2, -4, -7, -9, -15, and -21 cytokine receptors. These cytokines stimulate the activation and modulate the proliferation and function of lymphocytes, and all except IL-9 are thought to be involved in the pathogenesis of rheumatoid arthritis (RA) [5].

CP-690,550 is a novel ATP-competitive inhibitor of JAK3, and is currently being investigated as a disease modifying therapy for RA [6]. The compound is currently in phase 2 and has completed a proof of concept study in RA patients. Characterizing the exposure-response relationship between CP-690,550 and the ACR20 was desirable for an informed phase 2b selection of doses and design [7]. Specifically, quantifying pharmacodynamic onset (hysteresis) and estimating the maximum drug effect were of key interest for selecting doses regimens and study duration.

The primary clinical endpoint for the response of RA to treatment is the ACR20. ACR20 stands for the American College of Rheumatology (ACR) response criterion of 20% improvement. The criterion is a composite of 7 sub-scales, which assess swollen joints, tender joints, pain, the patient's and physician's global assessments of arthritis, patient's self-addressed disability, and modulation in C-reactive protein. A patient is denoted an ACR20 responder at a clinic visit if the patient demonstrates at least a 20% improvement from baseline in tender and swollen joint counts and at least a 20% improvement in three out of the other five sub-scales listed above. A patient is considered a non-responder otherwise. Responder status was used as the discrete clinical endpoint, which was linked to exposure using the LV modeling approach described below.

Methods

Data

Model development was supported using data from a parallel group phase 2a proof of concept study, which was randomized, double-blinded, and placebo-controlled [8]. This study investigated placebo and 5, 15 and 30 mg BID of CP-690,550 administered orally in 264 RA patients. Only 254 patients had data that could be included in the modeling analysis. Assigned treatment continued for 6 weeks, with 6 weeks of open-label post-treatment follow-up. ACR20 responder status was assessed at Weeks 1, 2, 4, and 6 during the assigned treatment phase. Only data from this (double-blind) phase were considered in the model fitting.

Indirect latent variable response model—concepts

Indirect response models provide a semi-mechanistic framework for linking pharmacodynamic (PD) responses to plasma concentrations (PK) and are useful when the PD and PK are not in equilibrium (the PD peaks or nadirs are not aligned temporally with the maximum drug concentration). Indirect response models are well characterized in the literature [9]. In general, these models can be represented through the generic differential equations,

$$\frac{dR}{dt} = k_1 u(t) - k_2 v(t) R(t), \quad R(t=0) = \frac{k_1}{k_2} = R_0, \quad (1)$$

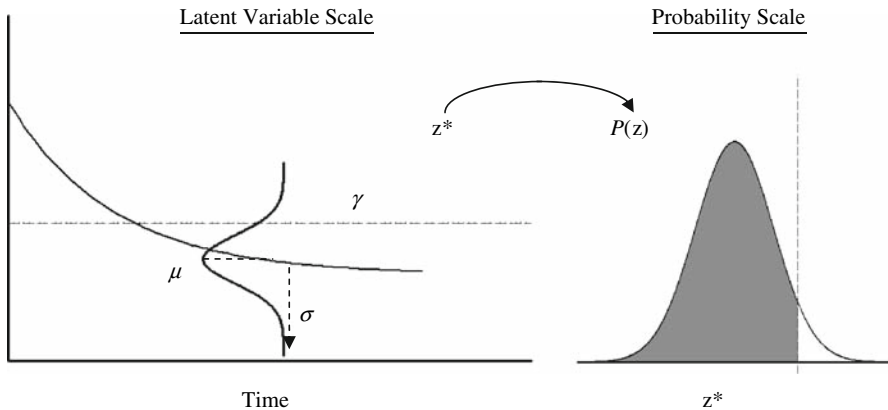


Fig. 1 An illustration depicting the mapping between the latent variable scale and the probability scale. As the mean of the latent variable falls below a threshold, γ , the amount of the latent variable distribution below the threshold increases. The fraction of the distribution below the threshold (calculated using Eq. 5) corresponds to the probability of a positive response ($z = 1$)

where k_1 is a zero-order production rate, k_2 is a first-order elimination rate, and $R(t)$ is the model predicted response. The forcing functions, $u(t)$ and $v(t)$, can be stimulatory or inhibitory—e.g.,

$$u(t) \text{ or } v(t) = 1 \pm \frac{E_{\max} \cdot C_e(t)}{EC_{50} + C_e(t)}, \quad (2)$$

where $C_e(t)$ is the effect site concentration at time t . Equation 2 is reported typically in the literature with plasma concentration, $C_p(t)$.

For continuous PD data, the ‘statistical’ model can be represented,

$$y = R(t) + \varepsilon, \quad (3)$$

where y is the measured response variable and ε is the residual error variable. The dependence of y on subject-specific random effects (η ’s in NONMEM nomenclature) is suppressed for ease of exposition. The population parameters of this model are generally pharmacologically interpretable, and can be estimated using the ELS (extended least squares) objective function implemented in NONMEM [10].

Sometimes efficacy and often safety data are measured as discrete, ordered categorical responses. Familiar examples are pain/pain relief, dizziness, and somnolence [2, 11, 12]. The extension of indirect response models to ordered categorical data is motivated here by the concept of a LV [13]. A LV is an underlying, unobservable variable, which can be mapped into binary or ordered categorical responses through the probability mass between thresholds [14]. Figure 1 conceptually demonstrates this mapping. The LV is assumed to be a function of the indirect response mechanism and any acting placebo effects. Constructing the LV as a function of the indirect response thus yields a pharmacologically interpretable type of model, hereafter referred to as the indirect latent variable response model (ILVRM). Because only one LV is used in

this derivation safety/adverse event responses should be assumed to emanate from a single mechanism—not general adverse events. A simple ILVRM form is

$$z^* = R(t) + \sigma \varepsilon \quad (4)$$

where z^* is the continuous (unobservable) latent variable, $R(t)$ is the model prediction of LV response (Eq. 1) or a function of it, σ scales the residual variability, and ε is (unobservable) error. The form of Eq. 4 is similar to the continuous data case described above.

To construct an ILVRM for CP-690,550 and ACR20, the conceptual supposition was this: ACR20 is related to inflammation, which is a function of the modulated lymphocytes [15]. Let the observable ACR20 binary response be z , and consider inflammation as the latent variable z^* . From the supposition, as inflammation decreases a positive ACR20 response is more likely to be observed. That is, the response, z , tends to equal 1 as z^* falls below a threshold, γ . More formally, assume $\varepsilon \sim N(0, 1)$, then the probability of a positive ACR20 response is computed as

$$\begin{aligned} P(z = 1) &= P(z^* < \gamma) = \frac{1}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{\gamma} \exp\left[-\frac{(z^* - R(t))^2}{2\sigma^2}\right] dz^* \\ &= \Phi[(\gamma - R(t))/\sigma] = \Phi(q) \end{aligned} \quad (5)$$

where $\Phi(\bullet)$ is the cumulative normal distribution (the result of integrating over z^*). Essentially Eq. 5 states that the $P(z = 1)$ is related to the amount of the LV distribution (from the integral) below the threshold parameter, γ (see Fig. 1). This result is known as a probit model, and $\Phi^{-1}(\bullet)$ is the probit link function. The probit derivation is provided to explicate the concepts (because of familiarity with integrating the normal density), although it is rarely used in population PK/PD models due to the complexity of implementing it in NONMEM. (A cumulative normal probability function is not documented in NONMEM V. Approximations can be coded and implemented however [16].) Note that

$$q = \frac{\gamma - R(t)}{\sigma} = \frac{\gamma - R_0\kappa(t)}{\sigma} = \gamma - R'_0\kappa(t) = \gamma' - R'(t) \quad (6)$$

where $R_0 = k_1/k_2$ and $\kappa(t)$ is the time component of R scaled by R_0 . Equation 6 reflects the lack of identifiability between γ , R_0 and σ . Without loss of generality, σ can be arbitrarily fixed to 1. Note that even though R is not directly measured, R_0 cannot be scaled to 1; estimation of R'_0 is necessary for correct estimates of k_2 [17].

A more familiar stochastic form is that of logistic regression. Assuming that ε is distributed according to the logistic density, then the logistic framework for the binary response case can be constructed as

$$P(z = 1) = P(z^* < \gamma) = \Psi(q) = [1 + \exp(q)]^{-1}, \quad (7)$$

where $\Psi(\bullet)$ is the familiar logistic (cumulative distribution) function. The logistic density has a mean of 0, a variance of $\pi^2/3$, and is similar to the t -distribution with

9 degrees of freedom. The binary framework, either probit or logit, can easily be extended for ordered categorical data (see Appendix A).

The logistic model was used to link CP-690,550 and ACR20 for this case study, and the probabilities defined in Eq. 7 were used to construct the likelihood. An individual's conditional likelihood (conditioned on the random effects) was constructed as,

$$l(\mathbf{z}|\boldsymbol{\eta}) = \prod_{j=1}^n [\Psi(q_j)]^{z_j} [1 - \Psi(q_j)]^{1-z_j}, \quad (8)$$

which assumes independent observations, indexed by j , within a subject. Assuming $\boldsymbol{\eta}$ is normally distributed, the Laplace approximation was used to approximate the integral for the marginal likelihood, which facilitated estimation in NONMEM V. Model predictions (marginal expectations or population means) were calculated using the sample mean Monte Carlo method,

$$\begin{aligned} E(\mathbf{z}) &= \int_{\Re} E(\mathbf{z}|\boldsymbol{\eta})\phi(\boldsymbol{\eta})d\boldsymbol{\eta} = \int_{\Re} \Psi(q|\boldsymbol{\eta})\phi(\boldsymbol{\eta})d\boldsymbol{\eta} \\ &\cong \frac{1}{M} \sum_{k=1}^M \Psi(q|\boldsymbol{\eta}_k^*) = \frac{1}{M} \sum_{k=1}^M P(z = 1|\boldsymbol{\eta}_k^*) \end{aligned} \quad (9)$$

where k indexes the sample of $\boldsymbol{\eta}^*$ from a normal distribution ($\phi(\bullet)$) with 0 mean and variance-covariance $\boldsymbol{\Omega}$, and M , the number of samples, is sufficiently large.

Exposure-response modeling using ILVRM

The concepts described above were used to formulate the ILVRM model, which linked CP-690,550 exposure to ACR20 response. The general model form implemented was

$$\text{logit}[P(z = 1)] = \gamma - f_p(t) - R(t) + \eta \quad (10)$$

where

$$f_p(t) = \beta \exp(-k_{plc}t) \quad (11)$$

is the placebo sub-model, γ represents the latent variable threshold parameter, $R(t)$ represents the drug effect as a function of time, and η is the subject-specific random effect. (The framework in Gibbons and Hedeker for generalized linear mixed effect LV models is extended here to generalized nonlinear mixed effect LV models [12].) Four typical pharmacological assumptions for the drug effect ($R(t)$) were postulated and fitted: inhibition of production (k_{in}), stimulation of degradation (k_{out}), direct action (dir), and pharmacokinetic (effect-site) delay (k_{eo}). The non-drug component of the model (the placebo sub-model and γ) was parameterized identically for all the different models. The parameters in the drug effect component differed according to the assumed pharmacologic model (see below).

Concentration-response models

A PK model was necessary to fit the concentration-response (C-R) models. A nonlinear mixed effects analysis was performed on available phase 1 single and multiple dose tolerability studies (results not published). A population one-compartment model with first order absorption fit these PK data adequately (results not shown). The parameter estimates from this fitting were $k_a = 2.12 \text{ h}^{-1}$, $CL/F = 24.4 \text{ l/h}$, and $V/F = 105 \text{ l}$ ($t_{1/2} = 3 \text{ h}$). This PK model was implemented in the fitting of the phase 2a PD data. Including the random effects in the C-R models neither improved the model fits nor explained (reduced) the PD variability in the fits. Additionally, inclusion of these variance components inflated the model run approximately 4-fold. For these reasons, the PK random effects were omitted from the analyses (see Sheiner et al. [2]) for more rationale).

The forcing functions used in the k_{in} , k_{out} , dir , and k_{eo} C-R models were:

$$k_{in}: u(t) = 1 - \frac{I_{\max} \cdot C_p(t)}{E_{50} + C_p(t)}, \quad v = 1, I_{\max} = 1; \quad (12)$$

$$k_{out}: u = 1, v(t) = 1 + \alpha \cdot C_p(t); \quad (13)$$

$$dir: u(t) = 1 - \frac{I_{\max} \cdot C_p(t)}{E_{50} + C_p(t)}, \quad v = 1, k_1 \rightarrow \infty, k_2 \rightarrow \infty, \frac{k_1}{k_2} \rightarrow E_0; \quad (14)$$

$$k_{eo}: \text{As } dir, \text{ except } u(t) = 1 - \frac{I_{\max} \cdot C_e(t)}{E_{50} + C_e(t)},$$

$$\frac{dC_e(t)}{dt} = k_{eo}(C_p(t) - C_e(t)). \quad (15)$$

Numerical integration was performed using the differential equation solver in NONMEM V (\$DES subroutine) to yield $R(t)$. ACR20 measurements were assumed to be measured at trough concentrations, and all patients were assumed compliant with medication administration for the fitting of these models. The dir and k_{eo} models are similar in form to those described in Sheiner et al. [2].

As previously stated, these models were developed in order to design a phase 2b dose ranging study. However, little time between receiving data from the proof of concept study to finalizing the phase 2b study protocol was available. To impact the design, the modeling would need to be completed and simulations would need to be performed in a relatively narrow timeframe. Concentration-response models were anticipated to be costly in time to develop and simulate due to large datasets. For example, numerous dosing data records were necessary to fit the C-R models; the proof of concept study modeled here consisted of 6 weeks, and the drug was administered twice a day (BID). Moreover, indirect C-R models required numerically solving differential equations, which combined with lengthy patient data, resulted in exorbitant run times. Surrogate models with shorter run times were expected to be more efficient for fitting and simulating, thereby speeding decision making.

To this end, the semi-mechanistic process was approximated by deriving an indirect response model, which used dose as a measure of exposure. Concentration was anticipated to be relatively constant so that the dose–response (D-R) model parameters

would be consistent with respect to the C-R model parameters, thereby maintaining model interpretation. These D-R models eliminated the need for dose administration times and solving differential equations. In parallel, the C-R models above were developed and the predictions were eventually compared graphically to those of the D-R models to verify the appropriateness of (similarity to) the D-R models. The parameter estimates were also compared between the two exposure measures to assess similarity of interpretation, such as rate of drug onset (e.g., similarity of k_2 estimates). The D-R models are detailed in the following sub-section.

Dose-response models

The four pharmacological models, k_{in} , k_{out} , dir , and k_{eo} were derived by inserting the dose strength into the forcing functions $v(\bullet)$ or $u(\bullet)$. The forcing functions for the four models were:

$$k_{in}: u = 1 - \frac{I_{\max} \cdot D}{E_{50} + D}, \quad v = 1, I_{\max} = 1; \quad (16)$$

$$k_{out}: u = 1, v = 1 + \alpha \cdot D; \quad (17)$$

$$dir: u = 1 - \frac{I_{\max} \cdot D}{E_{50} + D}, \quad v = 1, k_1 \rightarrow \infty, k_2 \rightarrow \infty, \frac{k_1}{k_2} \rightarrow R_0; \quad (18)$$

$$k_{eo}: \text{As } dir, \text{ except } u = 1 - \frac{I_{\max} \cdot D_e}{E_{50} + D_e}, D_e = D \cdot [1 - \exp(-k_{eo}t)]; \quad (19)$$

where D represents the dose, I_{\max} is the maximum drug effect, E_{50} is the dose that yields half of I_{\max} , α is the slope parameter (related to a pharmacodynamic steady-state ED_{50}), k_1 and k_2 are the rate parameters described in Eq. 1, and k_{eo} is the “pharmacokinetic” equilibration parameter [18]. These forcing functions are similar to those used in the C-R models, except these are functions of dose which is constant over time.

The closed form of Eq. 1,

$$\begin{aligned} R(t) = & k_1 \exp\left(-k_2 \int_0^t v(\lambda) d\lambda\right) \left(\int_0^t \exp\left(k_2 \int_0^\tau v(\lambda) d\lambda\right) u(\tau) d\tau\right) \\ & + R_0 \exp\left(-k_2 \int_0^t v(\lambda) d\lambda\right) \end{aligned} \quad (20)$$

was used to derive the dose-effect ($R(t)$) sub-models of the D-R models. Since the covariate dose is not a function of time, the integrals in Eq. 20 are tractable. Integrating the forcing functions yield the following dose-effect sub-models:

$$k_{in}: R(t) = R_o \left\{ \exp(-k_2 t) + \left(1 - \frac{D}{E_{50} + D} \right) [1 - \exp(-k_2 t)] \right\} \quad (21)$$

$$k_{out}: R(t) = R_o \left\{ \exp(-k'_2 t) + \frac{k_2}{k'_2} [1 - \exp(-k'_2 t)] \right\},$$

$$k'_2 = k_2 (1 + \alpha \cdot D) \quad (22)$$

$$dir: R(t) = -\frac{E_{\max} \cdot D}{E_{50} + D} \quad (23)$$

$$k_{eo}: R(t) = -\frac{E_{\max} \cdot D_e}{E_{50} + D_e} \quad (24)$$

where the parameter, E_{\max} , represents the maximum drug effect. These sub-models were input into Eq. 10 to model the ACR20 responses. Nonidentifiable model parameters were grouped in the drug sub-models and the overall models to maintain identifiability (e.g., $E_{\max} = R_o \times I_{\max}$). Example NONMEM code for the k_{out} model is provided in Appendix C.

The explicit drug-effect solutions provide some insight to the analyst. The k_{in} model applies an exponential delay to an E_{\max} -type model. The k_{out} model applies a dose-dependent exponential delay to a similar E_{\max} -type model as in the k_{in} model ($R_o/(1 + \alpha D)$ is an E_{\max} -type model, where α is interpreted as an inverse of E_{50}). The k_{eo} model applies an exponential delay to dose within an E_{\max} -type model. Essentially, the hysteresis can be interpreted through these three separate applications of the exponential delay. Additionally, at sufficiently large t , all these models converge to the same E_{\max} -model form (albeit with different parameterizations and estimates).

Results

The D-R and C-R model fits by week are displayed in Figs. 2 and 3, respectively. Careful examination of these figures, as well as tabular comparisons between observed and predicted, indicated that the k_{out} and k_{eo} models better fit the 5 mg response at week 1 and week 6. The objective functions are listed in Table 1. The objective functions of the k_{out} and k_{eo} models were less than the k_{in} and dir models as well (note that these models are not hierarchical, although these can be related to a larger model (see Hutmacher et al. [17])). A treatment related delay in (or onset of) response, in addition to the placebo time effect, was concluded to be an important model component (based on the comparisons discussed above). That is, the data supported the ILVRM scenarios, which postulated different hysteresis mechanisms.

The parameter estimates and the estimated asymptotic standard errors (ASE) from the four D-R and C-R model fits are also displayed in Table 1. Comparing the D-R and C-R models within model type, the potency parameters, α and E_{50} , are different, since concentration and dose operate on different scales (ng/ml and mg). However, most of the other parameter estimates are within a decimal point. The k_{in} model demonstrates the least similarity, yet the parameter estimates with greatest relative differences, γ and k_2 , are still not discrepant enough to differentiate the C-R and D-R fits graphically

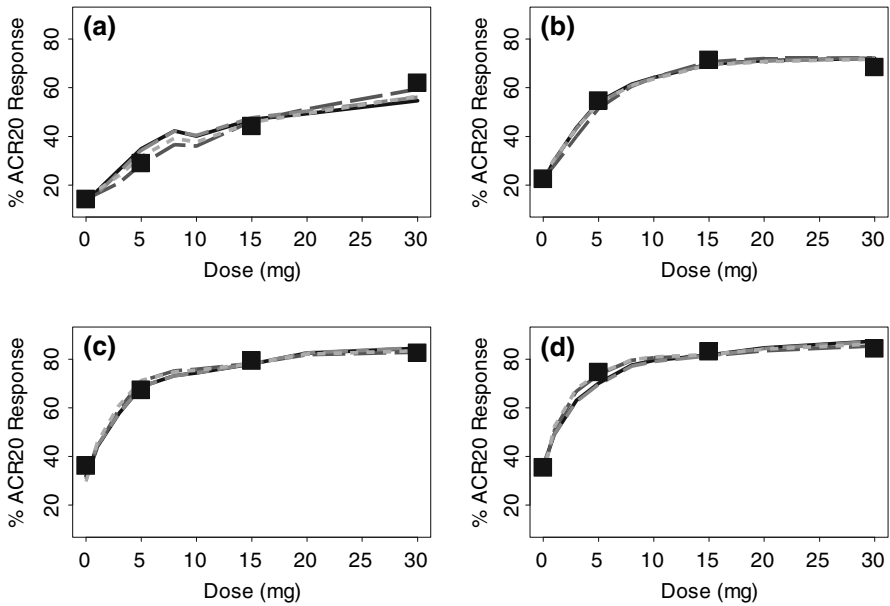


Fig. 2 Observed ACR20 mean responses (■) and D-R model predictions for the k_{in} (—), k_{out} (---), dir (- · -), and k_{eo} (·····) models versus dose by week: (a) Week 1, (b) Week 2, (c) Week 4, and (d) Week 6

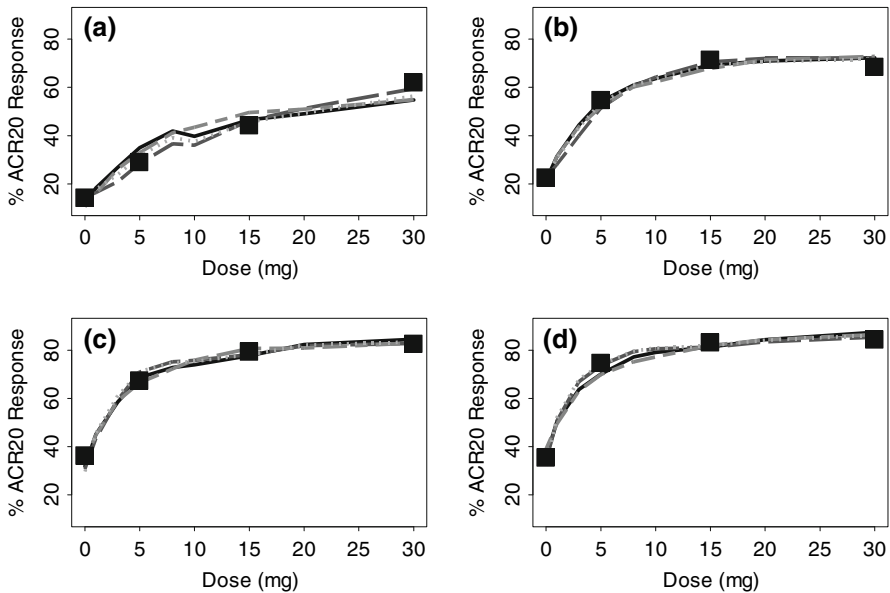


Fig. 3 Observed ACR20 mean responses (■) and C-R model predictions for the k_{in} (—), k_{out} (---), dir (- · -), and k_{eo} (·····) models versus dose by week: (a) Week 1, (b) Week 2, (c) Week 4, and (d) Week 6

Table 1 Parameter estimates and standard errors for the concentration- and dose-response models

Model/Parameter	k_{in}		k_{out}		dir		k_{eo}	
	C-R	D-R	C-R	D-R	C-R	D-R	C-R	D-R
$\gamma(\text{lg})$	3.79 (0.798)	3.62 (0.685)	3.10 (0.704)	3.09 (0.660)	-0.766 (0.432)	-0.767 (0.428)	-1.12 (0.414)	-1.12 (0.482)
$\beta(\text{lg})$	4.58 (1.79)	4.56 (1.68)	3.71 (1.20)	3.71 (1.02)	5.27 (1.03)	5.27 (1.02)	3.63 (0.976)	3.63 (1.12)
$k_{plc}(\text{wk}^{-1})$	0.611 (0.294)	0.608 (0.271)	0.608 (0.275)	0.610 (0.262)	0.693 (0.207)	0.695 (0.207)	0.682 (0.290)	0.683 (0.309)
$\ln(R_o)$	1.52 (0.180)	1.48 (0.164)	1.40 (0.172)	1.40 (0.165)	-	-	-	-
$\ln(E_{\max})$	-	-	-	-	1.47 (0.165)	1.47 (0.162)	1.46 (0.148)	1.46 (0.159)
$\ln(k_2)$	0.944 (0.901)	0.931 (0.897)	-1.67 (1.26)	-1.68 (1.03)	-	-	-	-
$\ln(k_{eo})$	-	-	-	-	-	-	-1.51 (0.793)	-1.51 (1.84)
$\ln(E_{50})$	2.48 (0.649)	1.47 (0.548)	-	-	1.18 (0.531)	1.53 (0.528)	1.74 (0.697)	0.515 (1.58)
$\ln(\alpha)$	-	-	-1.95 (1.11)	-0.717 (0.941)	-	-	-	-
ω^2	4.23 (0.969)	4.22 (0.963)	4.39 (1.00)	4.39 (1.00)	4.20 (0.965)	4.19 (0.952)	4.36 (0.982)	4.36 (0.997)
OBJ	944.060	944.037	938.735	938.743	944.233	944.234	940.070	940.074

The lg represents units on the logit scale

Quantities in parentheses (●) are estimated asymptotic errors

OBJ represents the resulting minimized objective function from NONMEM

The time scale for rate constants is in wk^{-1} ; potency in C-R models is in ng/ml and mg for DR models

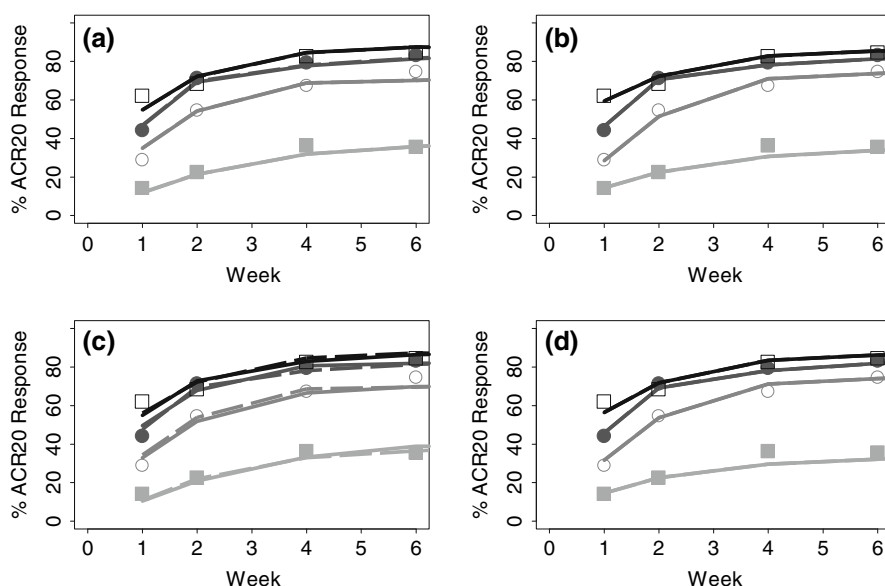


Fig. 4 Comparison of the C-R and D-R model predictions versus week by dose: (■) represents placebo, (○) represents 5 mg BID, (●) represents 10 mg BID, and (□) represents 30 mg BID

(and within simulation error). The model predictions (using Eq. 9) by dose over time are displayed in Fig. 4. The predictions are nearly identical between the C-R and D-R models within each pharmacological model type. Figure 5 displays the observed data and model predictions as a function of dose at week 6, the final clinic visit. The interpolations between doses are also nearly indistinguishable for the different exposure measures. Essentially, the D-R or C-R models were interchangeable with respect to BID regimen prediction. Thus BID dose selection could be achieved using the D-R models, which required less than 0.01 fold of computing time (note that the PK components of the *dir* and k_{eo} C-R models could be computed using an explicit solution, which would reduce the computing time to nearly that observed with the D-R models). With respect to inference, generally the ASEs for the C-R models were bigger for the k_{in} and k_{out} models, smaller for the k_{eo} model, and nearly identical for the *dir* model compared to the D-R model. Further study of the change in the ASE and the corresponding inferences by including these PK data would be interesting. However, this work is outside the scope of this manuscript.

The exchangeability of the D-R and C-R *dir* models for prediction and inference is intuitive (see below). The ACR20 responses were assumed to be measured at the trough concentrations, and no interindividual PK random effects were implemented in the concentration model. For these reasons, the dose value and the trough concentrations at steady state were identical, up to a scale factor (this statement is valid for all linear PK models when the typical individual PK profile is used and measurements are made at identical times across visits for all the patients). This scale factor was absorbed into the E_{50} during estimation. Since CP-690,550 PK achieved steady state prior to the

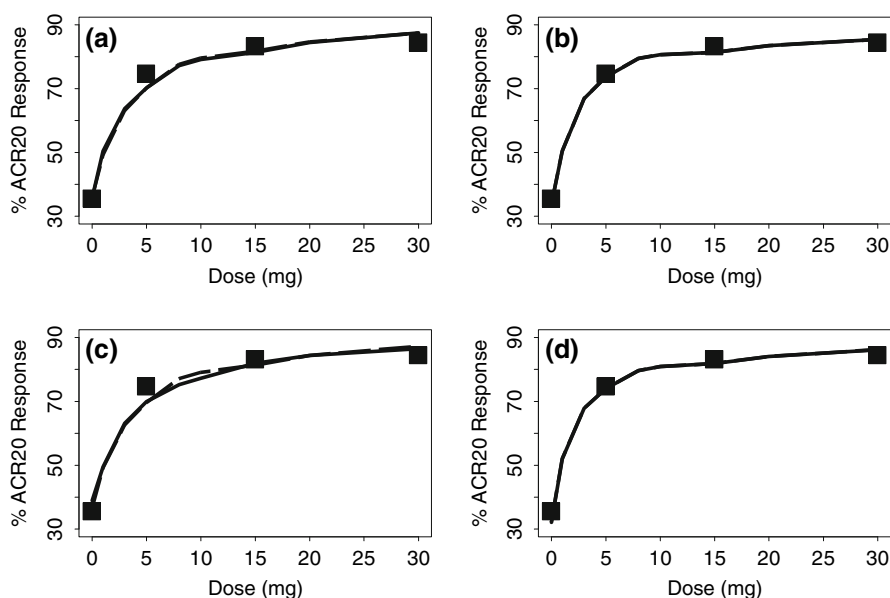


Fig. 5 Comparison of the C-R (—) and D-R (---) model predictions and observed mean responses (■) versus dose at week 6, the final clinic visit

first ACR20 measurement at 1 week, the differences between the D-R and E-R models were negligible.

The D-R and C-R k_{eo} models were also very similar. This similarity was also intuitive in retrospect. Since the typical individual profile was used and the PK half-life was short relative to the dosing interval, the trough effect site concentration, C_e , was nearly a scalar multiple of the effective dose, D_e . Appendix B demonstrates this similarity mathematically. Because of the half-life is relatively short, the difference between C_e and D_e is within a decimal point at each trough, and was thus not meaningful from a modeling perspective. The D_e and trough C_e trajectories, scaled by the respective E_{50} estimates, are plotted in Fig. 6 and are superimposable. It should be noted (and as a reviewer indicated) that the estimate of the k_{eo} parameter is 0.223 wk^{-1} , which is unrealistic for an effect-site (PK equilibration) type model. This estimate casts doubt about the applicability of this model to this mechanism, where as the k_{out} model maintains a more realistic pharmacologic interpretation.

Sometimes consideration of alternative regimens is desirable when planning studies or assessing dosing strategies. The data considered here were collected under BID administration, and so any prediction of an alternative regimen, such as TID or QD, would be an extrapolation. Intuitively, only the C-R models were (and are) reliable for predicting regimen. Figure 7 displays the model predictions for the BID arm and the extrapolations for some of the models to a QD regimen (for illustration) as a function of total daily dose at week 6. The k_{eo} model had similar predictions to the k_{out} model and was omitted for clarity. The k_{out} (and k_{eo}) model predicted similarly for BID and QD. However, total daily dose did not provide similar predictions for the k_{in} and

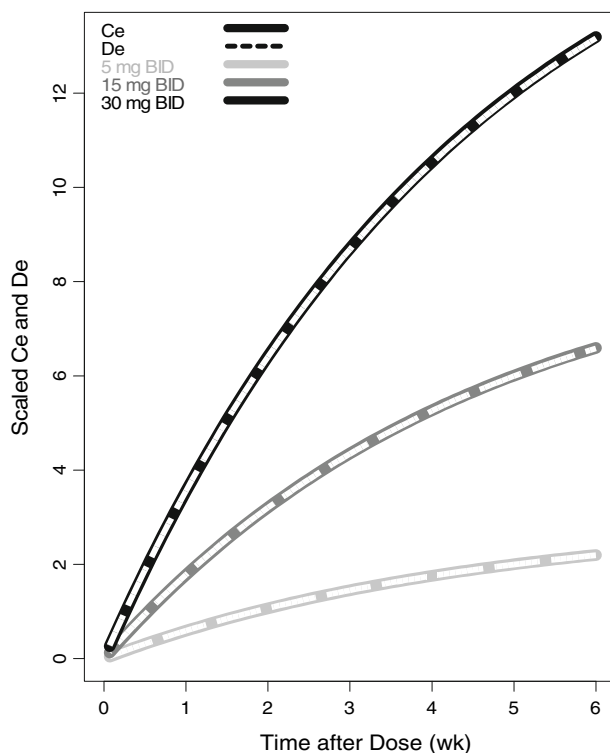


Fig. 6 Comparison over time of the trough effect site concentrations (C_e) and the effective dose (D_e), scaled by the respective E_{50} 's

dir models. The k_{in} model showed a slight reduction in ACR20 response for the QD regimen, and the *dir* model demonstrated a dramatic decrease.

Discussion

As a case study to demonstrate the ILVRM concepts, four pharmacologic models were developed for a JAK3 inhibitor administered to RA patients. Because of time constraints in planning a phase 2b study, efficient modeling and simulation strategies were considered. Concentration-based models require imputing dosing histories, and numerically solving differential equations can result in exorbitant model run times. To this end, exposure-response models using dose were derived and compared to corresponding C-R models.

The D-R and C-R models were similar in prediction and interpolation between doses within the BID regimen. Most likely, the similarities resulted from the interaction of some key conditions: the hysteresis between exposure and response was large relative to the effective PK half-life; CP-690,550 PK achieved steady-state within a couple of days; the first PD measurement was after a week of dosing; and the interindividual variation in PK parameters was not significant when added to the C-R models.

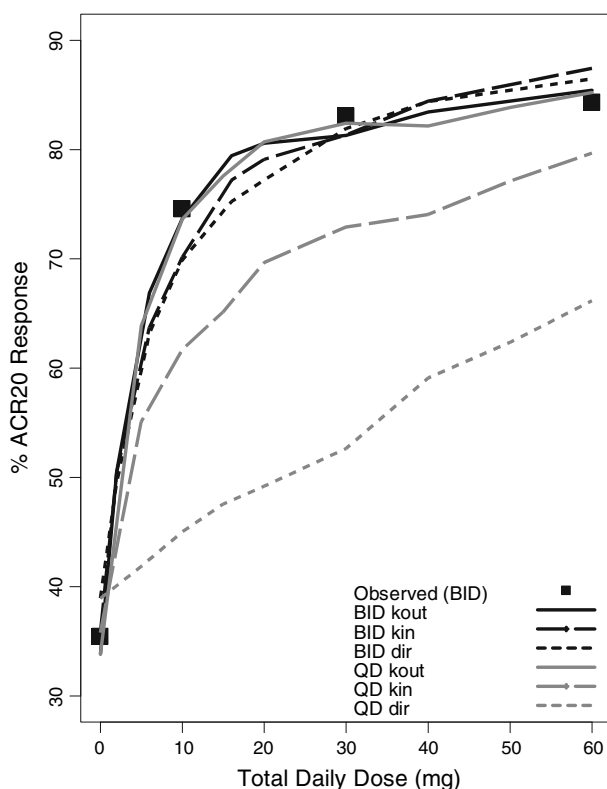


Fig. 7 C-R model predictions of the ACR20 responses versus total daily dose at week 6 for BID and QD administrations. The k_{eo} model predicted similarly to the k_{out} model for BID and QD at the doses considered, and thus was not plotted for clarity

If the variation in the PK parameters had been significant or these other conditions had not occurred, the degree of similarity would have likely decreased. Other approaches to reconcile the differences could then have been tested. An exponential term with a rate constant on dose could have been added, where the rate constant was tied to the rate of achieving steady state PK. If PK variability had been significant, AUC—a more individual specific function of dose—could have been used as the exposure measure. Note that the D-R model was conceptualized using the C-R model formulation, and its utility derives from this relation. Without the C-R models and derivations based on ILVRM, empirical models would likely have been selected. Pharmacological interpretations and predictions of alternative regimens might never have been realized.

Responses from QD administration can obviously be predicted from the C-R models fit to BID data. However, no simple mapping function existed (or generally exists) to predict QD results directly from BID results—e.g., halving the total daily dose. Concentrations from a QD regimen had to be simulated and input into the model in order to calculate the C-R model predictions. Clearly, prediction of the QD regimen would be problematic using D-R models fit to BID data. The D-R models would need to be fit to data following QD administration, and a separate set of parameters would

need to be estimated, in order to extrapolate. This is the inherent limitation of the D-R models.

Semi-mechanistic (indirect response) models are prevalent for continuous data. These models incorporate pharmacodynamic onsets (potentially dose dependent), maintain pharmacologic interpretations, and force feasible extrapolations, all of which are desirable from a modeling and simulation perspective. Model-based evaluation of hysteresis could be critical for indications in which onset of effect is a clinical endpoint, especially if a loading dose is desirable. Yet, empirical models are fit typically to binary and ordered categorical data. Formulation of empirical models ignores the drug's pharmacology. Ignoring the pharmacology can result in difficult interpretation. In Hutmacher et al. [4], the CAUC model obscured the interpretation of the observed weight effect between onset and potency. Delay in onset or differences in potency have vastly different implications when considering dosing strategies. Ultimately, the pharmacological processes that underpin ordered categorical (quantal) responses do not change just because the responses are discrete. The underlying drug mechanisms (i.e., binding to receptors, modulating cascades of events) are unaffected by the quantal nature of measurement (imprecise measurement device). Thus, pharmacologically interpretable models and methods should still be sought.

The ILVRM framework developed here supports these mechanistic-based models for better interpretation, prediction, and extrapolation of discrete responses. A continuous underlying process is hypothesized, such as inflammation or a general pathway. This postulated mechanism is structured using an indirect response model (or effect compartment) and is functionally related to a LV. The LV facilitates parameterization and model form and is used to map the probability of a response by using estimated thresholds. As a result, the discrete responses can be related to exposure according to a posited mechanism.

Potentially, these concepts and models could provide the foundations for linking continuous biomarker outcomes, discrete clinical endpoints, and even pre-clinical experimental data. Such models could highlight consistencies and differences throughout stages of development and thus better manage the knowledge inherent in this aggregate data.

Acknowledgements We would like to thank Dr. Raymond Miller for his kindly review and helpful comments.

Appendix A

Ordered categorical responses (Ordinal)

For K levels, there are $K + 1$ thresholds, where $\gamma_0 > \gamma_1 > \dots > \gamma_{K-1} > \gamma_K$, with $\gamma_0 = \infty$ and $\gamma_K = -\infty$. The probability for response k is

$$P(z = k) = P(\gamma_k < z^* \leq \gamma_{k-1}) = \Psi[(\gamma_{k-1} - R)/\sigma] - \Psi[(\gamma_k - R)/\sigma] \quad (25)$$

Without loss of generality, $\gamma_1 \equiv 0$. The individual and marginal likelihoods are constructed in a similar fashion as the binary response case.

Appendix B

Comparing C_e and D_e for the typical individual

Without loss of generality for linear PK models, a 1-compartment model with first order absorption is used to compare C_e and D_e . The trough concentration for the typical individual after n doses can be written as:

$$C(t_n = n \cdot \tau) = a_{ka} \frac{r_{ka} - (r_{ka})^{n+1}}{1 - r_{ka}} + a_{ke} \frac{r_{ke} - (r_{ke})^{n+1}}{1 - r_{ke}} + a_{keo} \frac{r_{keo} - (r_{keo})^{n+1}}{1 - r_{keo}} \quad (26)$$

where a_{ka} , a_{ke} , and a_{keo} are constants;

$$r_{ka} = \exp(-k_a \cdot \tau), \quad r_{ke} = \exp(-k_e \cdot \tau), \quad \text{and} \quad r_{keo} = \exp(-k_{eo} \cdot \tau);$$

τ is the dosing interval. When k_a and k_e are large relative to τ such that $r_{ka} \rightarrow 0$ and $r_{ke} \rightarrow 0$, then

$$\begin{aligned} C_e(t_n = n \cdot \tau) &\cong a_{keo} \frac{r_{keo} - (r_{keo})^{n+1}}{1 - r_{keo}} = a'_{keo} (1 - (r_{keo})^n) \\ &= a'_{keo} [1 - \exp(-k_{eo} \cdot n \cdot \tau)]. \end{aligned} \quad (27)$$

Thus, C_e at trough is approximately the scaled D_e , where

$$D_e(t_n = n \cdot \tau) = D[1 - \exp(-k_{eo} \cdot n \cdot \tau)]. \quad (28)$$

Appendix C

An excerpt of sample code (the \$PRED) for the k_{out} model

```
$PRED
KOUT = EXP (THETA (1) )           ; ***kout*** ;
ALPHA = EXP (THETA (2) )          ; ***α*** ;
RO = EXP (THETA (3) )             ; ***Ro*** ;
GAMMA = THETA (4)                 ; ***γ*** ;
BETA = THETA (5)                  ; ***β*** ;
KPLC = THETA (6)                  ; ***kplc*** ;
FP = THETA (5) * (EXP (-THETA (6) *WEEK) ) ; ***fp*** ;
VV = 1+ALPHA*DOSE                 ; ***v*** ;
R = RO* (EXP (-KOUT*VV*WEEK) +1/VV* (1-EXP (-KOUT*VV*WEEK) ) )
                                   ; ***R(t)*** ;
Q = BETA-A1-PBO+ETA (1)
```

```

EQ = EXP (BETA-A1-PBO+ETA (1) )
PZ1 = EQ / (1+EQ)      ; *** P(z = 1) *** ;
PZ0 = 1-PZ1            ; *** P(z = 0) *** ;
IF (DV.EQ.1) THEN
    TY = PZ1
ELSE
    TY = PZ0
ENDIF
Y = -2*LOG (TY)

```

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Elementary Osmotic Pump

FELIX THEEUWES

Abstract □ The elementary osmotic pump is a new delivery system for drugs or other active agents; it delivers the agent by an osmotic process at a controlled rate. Control resides in the: (a) water permeation characteristics of a semipermeable membrane surrounding the formulated agent, and (b) osmotic properties of the formulation. In its simplest embodiment, the system is constructed by coating an osmotically active solid agent with the rate-controlling, semipermeable membrane. This membrane contains an orifice of critical size through which solubilized agent is dispensed. The system can contain the agent in solid form at loadings higher than 90% of the total volume, and the agent can be delivered at rates several orders of magnitude higher than can be achieved by solution diffusion through polymeric membranes. The delivery rate, the fraction of total content delivered at zero order, and the system's delivery portal size have been calculated for delivery of a single compound. Experimental work verified the theory. The release rate from the system was found to be independent of outside agitation when the system is not deformed by shaking action, the pH of the environment, and delivery portal size for sizes within a specified range. The delivery rate from this system *in vitro* and in the GI tract of dogs was found to be equal.

Keyphrases □ Delivery systems, drug—elementary osmotic pump, controlled delivery rate, release characteristics, equations □ Drug delivery systems—elementary osmotic pump, controlled delivery, release rates, equations □ Osmotic pump—osmotic process, controlled rate drug delivery system, release rates, equations □ Membrane permeation—osmotic process, controlled rate drug delivery system

To achieve controlled administration of active agents, delivery mechanisms that can provide desired temporal patterns of the delivery rate have attracted great interest. The mechanism of delivering the active species by solution diffusion through a rate-controlling barrier has been found to be flexible and dependable (1) but limited in magnitude [maximum on the order of 0.2 $\mu\text{g}/(\text{cm hr})$] unless microporous barriers are used. To overcome these low rates and to permit the delivery of water-soluble species, an osmotic system was developed which delivers at membrane-controlled rates that can be several orders of magnitude higher than the drug diffusional rates. This new system is called the elementary osmotic pump (2). This paper describes such systems and gives examples of their characteristics for single-compound delivery.

The principles discussed here are applicable to systems using water or other solvents, but the reported work involved only water.

The elementary osmotic pump consists of an osmotic core containing the drug, surrounded by a semipermeable membrane with a delivery orifice. A cross section of the system is shown in Fig. 1.

When exposed to water, the core imbibes water osmotically at a controlled rate, determined by the membrane permeability to water and by the osmotic pressure of the core formulation. For a system at a constant internal volume, the device delivers, in any time interval, a volume of saturated solution equal to the volume of solvent uptake. The rate of solute de-

Annexure - 5

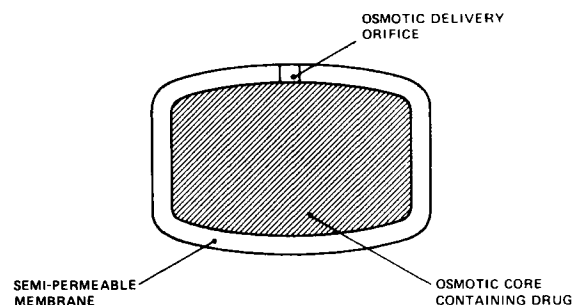


Figure 1—Elementary osmotic pump cross section.

livery by the system is constant as long as excess solid is present inside the device, but the rate declines parabolically toward zero once the concentration falls below saturation. The solution volume and mass solute delivery rate from the elementary osmotic pump can be predicted from the physicochemical parameters defining the system, as will be discussed. A typical release rate obtained from this system is illustrated in Fig. 2.

THEORETICAL

Delivery Rate—The delivery of agent from the system is controlled by the solvent influx across the semipermeable membrane, which in turn carries the agent to the outside (Fig. 1). Liquid transport by osmosis was qualitatively discussed by Starling (3), who identified the osmotic and hydrostatic pressure differences across capillary membranes as important factors governing transcapillary fluid transport. The process was rigorously treated in the field of nonequilibrium thermodynamics; Eq. 1, which describes the volume flux, dV/dt , across semipermeable membranes has been basic to the field of reverse osmosis (4):

$$\frac{dV}{dt} = \frac{A}{h} L_p (\sigma \Delta\pi - \Delta P) \quad (\text{Eq. 1})$$

where $\Delta\pi$ and ΔP are the osmotic and hydrostatic pressure differences, respectively, between the inside and outside of the system; L_p is the mechanical permeability; σ is the reflection coefficient; A is the membrane area; and h is the membrane thickness.

Equation 1 also describes the water flux into the elementary os-

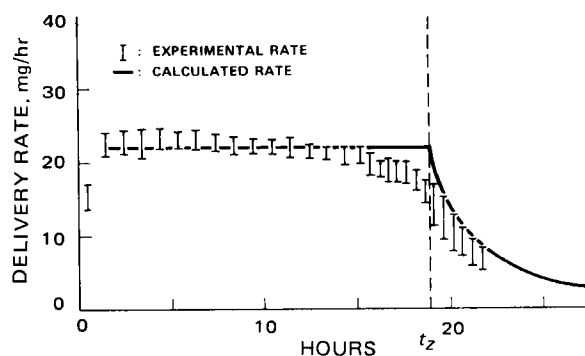


Figure 2—In vitro release rate of potassium chloride from elementary osmotic pumps in water at 37°. Key: \square , range of experimental data obtained from five systems; and —, calculated release rate.

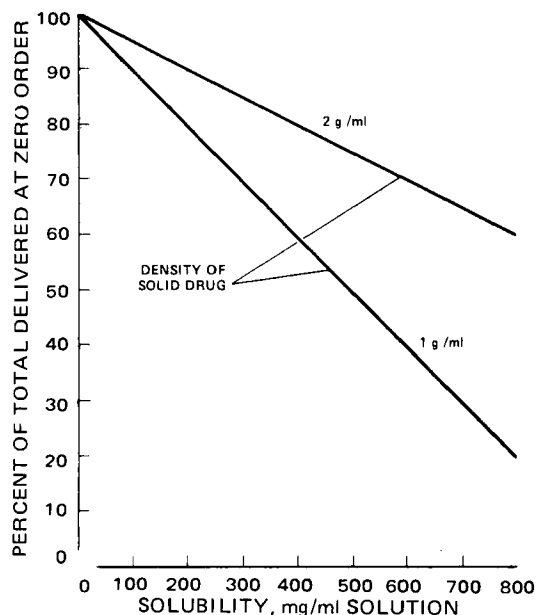


Figure 3—Fraction of drug content delivered from the elementary osmotic pump at constant rate.

otic pump (Fig. 1). The general expression for the solute delivery rate, dm/dt , obtained by pumping through the orifice is described by:

$$\frac{dm}{dt} = \frac{dV}{dt} C \quad (\text{Eq. 2})$$

where C is the concentration of compound in the dispensed fluid expressed per unit volume of solution.

Substituting Eq. 1 into Eq. 2 results in Eq. 3, which most broadly describes the solute delivery rate:

$$\frac{dm}{dt} = \frac{A}{h} L_p (\sigma \Delta \pi - \Delta P) C \quad (\text{Eq. 3})$$

As the delivery orifice increases, hydrostatic pressure inside the system is minimized as expressed by the condition $\Delta \pi \gg \Delta P$.

When the osmotic pressure of the formulation (π) is large compared to the osmotic pressure of the environment, π can be substituted for $\Delta \pi$. Equation 3 then reduces to a much simpler expression in which the constant k replaces the product $L_p \sigma$:

$$\frac{dm}{dt} = \frac{A}{h} k \pi C \quad (\text{Eq. 4})$$

Zero-Order Delivery Rate—The release rate from the elementary osmotic pump is zero order from $t = 0$ until a time t_z , at which time all of the solid in the core has dissolved and is described by:

$$\left(\frac{dm}{dt} \right)_z = \frac{A}{h} k \pi_s S \quad (\text{Eq. 5})$$

where S is the solubility, and π_s is the osmotic pressure at saturation.

The rate of dissolution of a single compound within the system is much larger than the rate of pumping as given by Eq. 5. For this reason, the concentration, C , can be replaced by the component solubility, S , from time $t = 0$ to $t = t_z$.

Nonzero-Order Release Rate—The nonzero-order release rate from the system (Eq. 4) is obtained by describing the concentration, C , as a function of time. For simplicity, the volume flux into the system is replaced by the symbol F :

$$F = \frac{A}{h} k \pi \quad (\text{Eq. 6})$$

and F_s represents the flux during the zero-order time and is related to F by:

$$\frac{F_s}{F} = \frac{\pi_s}{\pi} = \frac{S}{C} \quad (\text{Eq. 7})$$

By substituting Eq. 7 into Eq. 4, the nonzero-order release rate as a function of concentration is given by:

$$\frac{dm}{dt} = \frac{F_s}{S} C^2 \quad (\text{Eq. 8})$$

Beyond t_z , the mass, m , of component dissolved into the elementary pump volume, V , is given by:

$$m = CV \quad (\text{Eq. 9})$$

The change in mass at constant volume, V , causes a concentration change, dC/dt , given by:

$$\frac{dm}{dt} = -V \frac{dC}{dt} \quad (\text{Eq. 10})$$

The delivery rate, dm/dt , can be eliminated between Eqs. 8 and 10 as shown by:

$$-\frac{dC}{dt} = \frac{F_s}{VS} C^2 \quad (\text{Eq. 11})$$

The concentration, C , inside the system is obtained by integrating Eq. 11 from time t_z to t , when the concentration changes from S to C :

$$-\int_S^C \frac{dC}{C^2} = \frac{F_s}{VS} \int_{t_z}^t dt \quad (\text{Eq. 12})$$

Solving Eq. 12 and rearranging terms result in an expression for the concentration as a function of time:

$$C = \frac{VS}{V + F_s(t - t_z)} \quad (\text{Eq. 13})$$

Substituting Eq. 13 into Eq. 8 gives the release rate as a function of time, indicating the parabolic decline:

$$\frac{dm}{dt} = \frac{F_s S}{\left[1 + \frac{F_s}{V}(t - t_z) \right]^2} \quad (\text{Eq. 14})$$

The nonzero-order release rate can also be expressed as a fraction of the zero-order rate:

$$\frac{dm}{dt} = \frac{(dm/dt)_z}{\left[1 + \frac{1}{SV} \left(\frac{dm}{dt} \right)_z (t - t_z) \right]^2} \quad (\text{Eq. 15})$$

The delivery rate discussed in this section is the rate from the elementary osmotic pump when most of the contents are delivered by pumping. When the membrane is not ideally semipermeable, a fraction of the agent is delivered by diffusion through the membrane. The case involving both pumping and diffusion is treated in the Appendix.

Mass Delivered at Zero Order, m_z , and Zero-Order Delivery Time, t_z —For a total mass, m_t , contained in the core of the elementary osmotic pump, only an amount m_z is delivered at zero order, and an amount m_{NZ} is delivered at a parabolically declining rate given by Eq. 14. The amount m_{NZ} is the mass that just fills the internal volume of the system with a saturated solution, as shown by:

$$m_{NZ} = SV \quad (\text{Eq. 16})$$

The internal volume, V , of the system containing a pure component is related to the total mass, m_t , by the density, ρ , of the core by:

$$m_t = \rho V \quad (\text{Eq. 17})$$

The fraction not delivered at zero order is obtained from Eqs. 16 and 17 and given by:

$$\frac{m_{NZ}}{m_t} = \frac{S}{\rho} \quad (\text{Eq. 18})$$

Since the sum of m_{NZ} and m_z is equal to m_t , the fraction of the total mass delivered at zero order is given by:

$$\frac{m_z}{m_t} = 1 - \frac{S}{\rho} \quad (\text{Eq. 19})$$

The fraction of total device content expressed in percent calculated from Eq. 19 is shown in Fig. 3 for two different compound densities as a function of compound solubility.

The time t_z at which the mass m_z is delivered for an ideal system, with zero startup time, is obtained from:

$$\frac{m_z}{t_z} = \left(\frac{dm}{dt} \right)_z \quad (\text{Eq. 20})$$

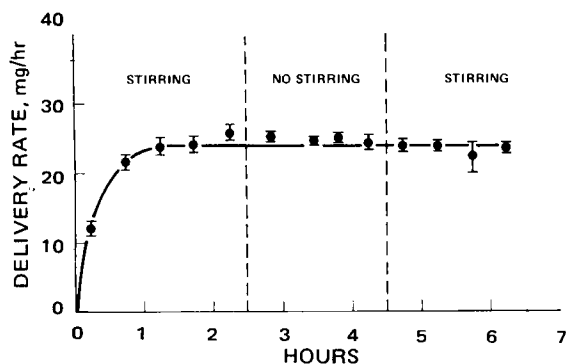


Figure 4—In vitro release rate of potassium chloride from elementary osmotic pumps in water at 37°. The vertical dashed lines indicate the time at which the systems were transferred from a stirred to a stagnant medium and back to a stirred medium. \pm represents the range of experimental data obtained from five systems.

Combining Eqs. 19 and 20 gives:

$$t_z = m_i \left(1 - \frac{S}{\rho}\right) \frac{1}{(dm/dt)_z} \quad (\text{Eq. 21})$$

Size of Delivery Orifice—The size of the delivery orifice must satisfy two conditions:

1. It must be smaller than a maximum size, A_{\max} , to minimize the contribution to the delivery rate made by solute diffusion through the orifice.
2. It must be sufficiently large, above a minimum size, A_{\min} , to minimize hydrostatic pressure inside the system that would affect the zero-order release rate in the following ways. Hydrostatic pressure within the system not only decreases the osmotic influx as seen from Eq. 1, but also it can increase the volume of the system. During the time that the system volume is increasing, the outflow would be smaller than the inflow, resulting in a depressed delivery rate.

Mathematically, these two conditions can be expressed by $A_{\min} \leq A_0 \leq A_{\max}$, where the cross-sectional area of the orifice, A_0 , is larger than or equal to a minimum value and smaller than or equal to a maximum value.

The minimum cross-sectional area can be estimated from Poiseuille's law (4):

$$A_{\min} = 5 \left(l \frac{dV}{dt} \frac{\eta}{\Delta P_{\max}} \right)^{1/2} \quad (\text{Eq. 22})$$

where dV/dt is the volume flux through the orifice, l is the length of the orifice, η is the viscosity of the dispensed solution, and ΔP_{\max} is the maximum hydrostatic tolerated pressure difference between the inside and outside of the device. The ΔP_{\max} is the pressure at which deformation of the membrane housing occurs or that is significant with respect to the osmotic driving pressure, whichever is smallest.

The maximum cross-sectional area allowed, A_{\max} , is obtained by imposing the condition that the diffusional contribution to the release rate must be a factor, F , smaller than the zero-order pumping rate as defined by Eq. 5. This condition is expressed by:

$$A_{\max} = \frac{l}{F} \left(\frac{dm}{dt} \right) \frac{1}{zDS} \quad (\text{Eq. 23})$$

in which D is the diffusion coefficient of the compound being delivered in the solvent within the orifice.

In practice, perfect membrane-controlled osmotic delivery has been obtained when $F \geq 40$, as will be discussed.

EXPERIMENTAL

Potassium Chloride Elementary Osmotic Pump Fabrication—Systems were prepared containing 500 mg of potassium chloride each, described by the following parameters: $V = 0.25 \text{ cm}^3$, $h = 0.025 \text{ cm}$, $A = 2.2 \text{ cm}^2$, $k\pi_s = 0.686 \times 10^{-3} \text{ cm}^2/\text{hr}$, $P = 0.122 \times 10^{-3} \text{ cm}^2/\text{hr}$, $S = 330 \text{ mg/ml}$, and $\rho = 2 \text{ g/ml}$.

The total mass was compressed in a hard tablet and the volume, V , was calculated assuming the density, ρ (5). The area, A , was calculated from the tablet geometry, and the membrane thickness

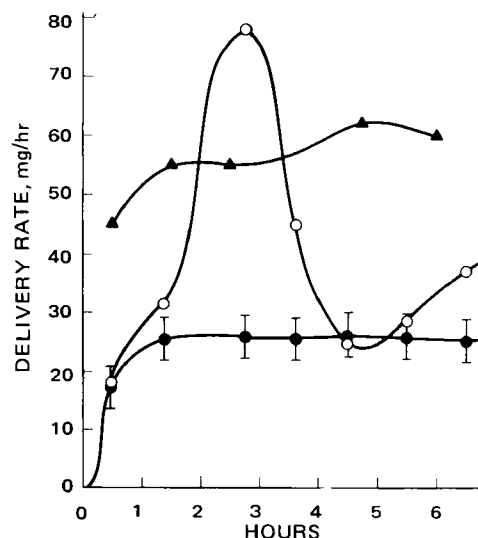


Figure 5—In vitro release rate of potassium chloride from elementary osmotic pump systems in water at 37°. Key: \pm , range of experimental data obtained from systems with cylindrical orifices of diameters 75, 128, 190, and 274 μm ; \circ , system with 435- μm orifice diameter; and \blacktriangle , system with 368- μm orifice diameter.

was measured using a standard thickness gauge. The solubility, S , at 37° was determined by electrical conductance measurements after dilution of the filtered saturated solution into the concentration range where a calibration curve was constructed.

The permeability coefficient, P , and the product, $k\pi_s$, were determined in a permeation experiment (4) where the membrane was placed in a diffusion cell separating water from the stirred saturated solution of potassium chloride. The permeability coefficient, P , was calculated, by measuring the salt transported across the membrane by electrical conductance, from an equation of the form of the second term of Eq. A3. The product, $k\pi_s$, was calculated from Eq. 6, where the volume flow was determined by the displacement of the meniscus of the saturated solution in a graduated cylinder mounted on the cell half containing the saturated solution during a time interval, Δt , measured with a stopwatch.

In Vitro Delivery Rate Measurements—The release rate from the systems was obtained by transferring each at regular, usually hourly, intervals from one test tube to the following and measuring the amount released in each test tube. All experiments were carried out at 37° in the fluids indicated on the figures. The potassium chloride systems were agitated with a stroke of 2.5 cm at a frequency of 0.5 stroke/sec for the experiments shown in Figs. 2, 4, 5, and 6. The larger phenobarbital sodium elementary osmotic pumps referred to in Fig. 7 were manually transferred to sequential flasks in which the liquid was stirred constantly.

Potassium chloride concentrations were measured by electrical conductance. Phenobarbital sodium concentrations were measured spectrophotometrically.

In Vivo Delivery Rate Measurements—Color-coded 500-mg

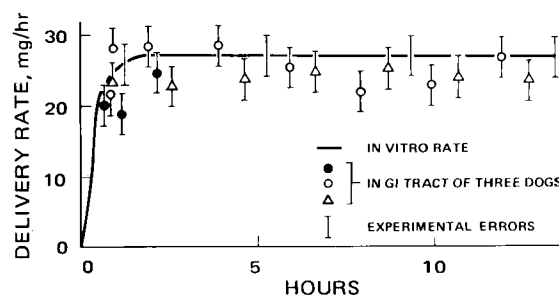


Figure 6—In vitro and in vivo release rate of potassium chloride from elementary osmotic pumps. Key: —, average in vitro rate from systems of the same batch; and Δ , \circ , \bullet , average release rate of one system in the GI tract of Dogs 1, 2, and 3, plotted at the total time period each system resided in the dog.

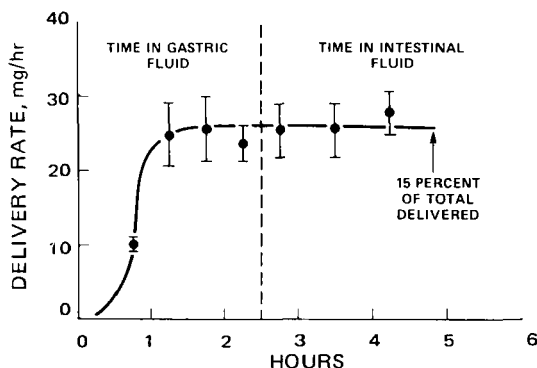


Figure 7—In vitro release rate of phenobarbital sodium from elementary osmotic pump systems in gastric and intestinal fluid USP without enzymes. The vertical dashed line indicates the time at which the systems were transferred from gastric to intestinal fluid. \pm represents the range of experimental data obtained from three systems.

potassium chloride elementary osmotic pump systems were administered to three dogs at recorded time intervals. The dogs were sacrificed, the devices were retrieved, and the *in vivo* rates were determined gravimetrically from the initial and final dry weights of each individual system.

RESULTS AND DISCUSSION

Predictability of Delivery Rate—For elementary osmotic pump systems containing 500 mg of potassium chloride and prepared as already described, the predicted pumping rate, as calculated from Eq. 5, was 20 mg/hr. By correcting for the 20% diffusional contribution, as shown by Eq. A4 (Appendix), the release rate was found to be 24 mg/hr.

When assuming one adjustable parameter, $(dm/dt)_z = 22$ mg/hr, as the observed experimental rate, the zero-order time, $t_z = 19$ hr, was calculated from Eq. 21. When using the experimental zero-order rate, the nonzero-order tail was calculated from Eq. 15 (solid line in Fig. 2). An identical curve was obtained by accounting for the diffusional contribution (treated in Appendix) by calculating the nonzero-order rate from Eqs. A5 and A13. The data are represented within the limits of experimental error by these equations. For simplicity, the system is well described by the equations applying to pumping when the diffusional contribution is not more than 20%.

Because of its osmotic action, the system exhibits two important characteristics which are described in the next two subsections.

Delivery Rate Is Independent of Outside Agitation—The release rates of five similar potassium chloride systems were measured sequentially in (a) stirred, (b) stagnant (no stirring), and (c) stirred media. The release rate was measured by the mass delivered during about 30-min intervals (Fig. 4). During stirring, the systems were moved up and down with a stroke of 2.5 cm and a frequency of 0.5 stroke/sec in water at 37°. The devices were kept immobile during the stagnant period. As can be seen in Fig. 4, the release rate under both conditions was identical.

Delivery Rate Is Independent of pH—Because of the semi-permeable characteristics of the membrane, ions are not readily exchanged across it and the formulation contained within the device can be programmed at a pH independent from its environment. A compound with a solubility that is highly pH dependent can be incorporated in the water-soluble salt form. During operation, the internal core of the elementary pump keeps the pH created by this salt form as its *in situ* created formulation. The delivery rate from the system, as explained previously, is governed by the osmotic pressure of the formulation and the water permeability of the membrane and is therefore independent of the pH of the environment.

As an example, the average release rate from three elementary osmotic pump systems delivering phenobarbital sodium in artificial gastric (pH 2) and intestinal fluid (pH 7.5) (without enzymes) is shown in Fig. 7. The release rate was independent of the pH of the delivery medium.

Delivery Rate Is Independent of Delivery Port Sizes within Predictable Limits—According to $A_{\min} \leq A_0 \leq A_{\max}$, the delivery rate should be independent of the delivery orifice size for sizes within the range expressed by Eqs. 22 and 23. For pharmaceutical dosage forms where the orifice length is on the order of the membrane thickness, $l = h \approx 25 \times 10^{-4}$ cm, $\eta = 1$ cps, $(dV/dt) \approx 0.1$ ml/hr, and $\Delta P \approx 1$ atm, the minimum orifice area calculated from Eq. 22 is on the order of $A_{\min} \approx 13 \times 10^{-8}$ cm². For a cylindrical hole, the diameter is then 4×10^{-4} cm—difficult or impossible to be drilled.

To find an operational delivery orifice, it is of practical importance to calculate only the upper size, A_{\max} , as defined by Eq. 23. The sizing factor, F , has been experimentally determined by measuring the release rate as a function of the hole size. In Fig. 5, the release rate from 500-mg potassium chloride elementary osmotic pumps is plotted for various hole sizes. Complete membrane-controlled delivery was observed for all hole diameters, 75, 128, 190, and 274×10^{-4} cm. At 368×10^{-4} cm and above, control over the delivery rate was lost. The transition from membrane control to the occurrence of diffusion and probably convection within the orifice was dramatic. No systematic trend in delivery was observed within the hole size range from 75 to 274 μ m.

The sizing factor, F , was calculated from Eq. 23 assuming A_{\max} as the orifice area corresponding to the 274- μ m diameter hole. The length of the passageway through the membrane was $l = 25 \times 10^{-4}$ cm; $(dm/dt)_z = 25$ mg/hr, as seen from Fig. 5; $S = 330$ mg/ml; and diffusion coefficient $D = 2 \times 10^{-5}$ cm²/sec (5). The sizing factor was found to be $F = 40$.

Delivery Rate in GI Tract Is Equal to In Vitro Rate—The elementary pump system can be broadly applied to controlled delivery. A number of pharmaceutical applications such as implants, inserts in body cavities, or oral delivery come to mind, since all of these applications provide an environment of constant water activity.

The system is of special interest in oral application because high, predictable delivery rates can be obtained independent of GI motility and the pH of luminal fluids. An additional benefit is the system's delivery of the drug in solution ready for absorption. Thus, the elementary osmotic pump is an *in situ* prepared liquid dosage form.

In the example shown in Fig. 6, the *in vivo* functionality of the system is demonstrated in the GI tract of dogs. Each experimental point represents the average *in vivo* release rate from each system during its total residence time in the GI tract. The data points are plotted at the total residence time observed for the device. The solid line is the *in vitro* release rate.

The *in vitro* delivery profile was measured for systems of the same batch in water at 37°. The average *in vivo* delivery rate was found to be systematically lower by about 10%. The *in vivo* data agree with the *in vitro* data within the combined experimental error of 20% (6).

CONCLUSIONS

1. The mode of operation of the elementary pump is well understood, and the *in vitro* delivery rate from the system can be accurately predicted.
2. The fraction of drug delivered at zero order can be predicted from the compound solubility and core density.
3. The delivery rate is independent of: (a) the pH of the environment, (b) the agitation of the environment, and (c) the size of the orifice for orifices within the predictable range.
4. The *in vivo* delivery rate from the system is essentially equal to the predictable *in vitro* delivery rate.

APPENDIX

The release rate from the elementary osmotic pump is the total mass delivered per unit time from this system. In practice, three mechanisms contribute to the delivery: (a) delivery by pumping, $(dm/dt)_p$, which was described previously; (b) delivery by diffusion through the orifice, $(dm/dt)_{DO}$; and (c) delivery by diffusion through the membrane, $(dm/dt)_{DM}$. The total delivery rate is then given by:

$$\left(\frac{dm}{dt}\right)_t = \left(\frac{dm}{dt}\right)_p + \left(\frac{dm}{dt}\right)_{DO} + \left(\frac{dm}{dt}\right)_{DM} \quad (\text{Eq. A1})$$

By design of the system, the diffusion through the orifice was selected to be negligible, as expressed by $A_{\min} \leq A_0 \leq A_{\max}$, and Eq. A1 reduces to:

$$\left(\frac{dm}{dt}\right)_t = \left(\frac{dm}{dt}\right)_P + \left(\frac{dm}{dt}\right)_{DM} \quad (\text{Eq. A2})$$

For most agents that have a high molecular weight and/or are ionic, the membrane will appear as ideally semipermeable and a negligible amount of agent will be delivered by diffusion through it.

When delivering low molecular weight substances and when the membrane is sufficiently solvated, the second term in Eq. A2 can become important. The total release rate (Eq. A2) is controlled by the same membrane and, as before, a zero-order and nonzero-order pattern will be observed.

Zero-Order Delivery by Pumping and Diffusion—The total zero-order rate is given by the sum of two terms: the pumping rate expressed by Eq. 5 and the diffusional term expressed by Fick's law:

$$\left(\frac{dm}{dt}\right)_{t,z} = \frac{A}{h} k \pi_s S + \frac{A}{h} P S \quad (\text{Eq. A3})$$

where P is the permeability coefficient. Equation A3 reduces to:

$$\left(\frac{dm}{dt}\right)_{t,z} = \frac{A}{h} S(k \pi_s + P) \quad (\text{Eq. A4})$$

which is of the same form as Eq. 5 for the ideal case.

In practice, the zero-order rate can be calculated from Eq. A4 or 5 after defining an effective $k \pi_s$ or solubility number.

Nonzero-Order Delivery by Pumping and Diffusion—The nonzero-order delivery rate is given by the sum of the pumping rate, Eq. 8, and the diffusional term:

$$\frac{dm}{dt} = \frac{F_s}{S} C^2 + \frac{A}{h} P C \quad (\text{Eq. A5})$$

To express dm/dt as a function of time, the concentration, C , inside the system must be expressed as a function of time. This can be done by solving the differential Eq. A6 derived from Eq. A5 by substituting again Eq. 10 for dm/dt :

$$-\frac{dC}{dt} = \frac{F_s}{VS} C^2 + \frac{AP}{Vh} C \quad (\text{Eq. A6})$$

Then substituting:

$$R = \frac{F_s}{VS} \quad (\text{Eq. A7a})$$

$$Q = \frac{AP}{Vh} \quad (\text{Eq. A7b})$$

into Eq. A6 results in:

$$\frac{dC}{C(RC + Q)} = -dt \quad (\text{Eq. A8})$$

Equation A8 can be integrated by fractions after identifying the

coefficients α and β as shown in:

$$\frac{1}{C(RC + Q)} = \frac{\alpha}{C} + \frac{\beta}{RC + Q} \quad (\text{Eq. A9})$$

Equalizing the coefficients of equal powers of C results in:

$$\alpha = \frac{1}{Q} \quad (\text{Eq. A10})$$

$$\beta = -\frac{R}{Q} \quad (\text{Eq. A11})$$

Substituting Eqs. A10 and A11 into Eq. A9 and substituting Eq. A9 into Eq. A8 result in:

$$\frac{dC}{QC} - \frac{R}{Q} \frac{dC}{(RC + Q)} = -dt \quad (\text{Eq. A12})$$

Equation A12 can be integrated from time t_z to t when the concentration changes from S to C . Also, replacing R and Q by their values given in Eq. A7 results in:

$$t - t_z = \frac{Vh}{AP} \ln \left(\frac{F_s \frac{C}{S} + \frac{AP}{h}}{\left(F_s + \frac{AP}{h} \right) \frac{C}{S}} \right) \quad (\text{Eq. A13})$$

Equation A13 does not give the concentration, C , as an explicit function of time for substitution into Eq. A5. From Eq. A13, C and C^2 can be tabulated as a function of time, and from these values the rate can be calculated using Eq. A5.

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ACKNOWLEDGMENTS AND ADDRESSES

Received February 19, 1975, from Alza Research, Palo Alto, CA 94303

Accepted for publication April 1, 1975.

The author thanks Mr. J. McCoy for his assistance in the experimental work and Dr. T. Higuchi, Dr. J. Windheuser, and Dr. A. S. Michaels for their discussions.

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International Journal of Pharmaceutics 259 (2003) 173–179

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Effect of hydrophilic polymers on the release of diltiazem hydrochloride from elementary osmotic pumps

D. Prabakaran, Paramjit Singh, Parijat Kanaujia, Suresh P. Vyas*

Drug delivery research laboratory, Department of Pharmaceutical Sciences, Dr. Harisingh Gour University, Sagar, M.P. 470 003, India

Received 13 December 2002; received in revised form 18 March 2003; accepted 28 March 2003

Abstract

Diltiazem hydrochloride (DLTZ) is a freely water-soluble drug, because of its higher aqueous solubility, the suitability of the drug with elementary osmotic pumps is restricted. Plain DLTZ elementary osmotic pump had shown higher release rate. Drug entrapment in polymer matrix or addition of release retardant materials (various polymers) can reduce the release rate of drug. In present study, effect of appropriate hydrophilic polymers (HP) on the release pattern was investigated. Ingredients of the system were optimized for parameters like drug:polymer ratio and amount of osmogen, for the desired release pattern. Two optimized formulations were selected for further characterization. Theoretical release rate of the formulations were also determined and compared. Different dissolution models were applied to drug release data in order to establish release mechanism and kinetics. Criteria for selecting the most appropriate model were based on best goodness of fit and smallest sum of squared residuals.

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Keywords: Osmotic pumps; Hydrophilic polymers; Diltiazem hydrochloride; Release kinetics

1. Introduction

Osmotic pumps are controlled drug delivery devices based on the principle of osmosis. A wide spectrum of osmotic devices are in existence, out of them osmotic pumps are unique, dynamic and widely employed in clinical practice (Santus and Baker, 1995; Singh et al., 1999). Osmotic pumps offer many advantages like they are easy to formulate and simple in operation, improved patient compliance with reduced dosing frequency, more consistent and prolonged therapeutic effect is obtained with uniform blood concentration

and moreover they are inexpensive and their industrial adaptability vis-a-vis production scale up is easy.

Elementary osmotic pumps essentially contain an active agent having suitable osmotic pressure, contained into a tablet, coated with a semipermeable membrane usually of cellulose acetate (Theeuwes, 1975). A small orifice is drilled through the coating by using LASER or high-speed mechanical drill. In fact, this system represents a coated tablet with an aperture. When exposed to an aqueous environment, the soluble drug within the tablet draws water through the semipermeable coating, resulting in formation of a saturated aqueous drug solution within the device. The membrane is non-extensible and increase in volume due to imbibition of water raises inner hydrostatic pressure, eventually leading to flow of saturated solution of active agent out of the device through small orifice. Solubility of drug in water plays a criti-

* Corresponding author. Tel.: +91-7582-26525; fax: +91-7582-26525.

E-mail addresses: spvyas@sancharnet.in, vyas_sp@rediffmail.com (S.P. Vyas).

cal role in functioning of osmotic pump. Typically the solubility of drug delivered by these pumps should be at least 10–15% (w/v).

The drug is pumped out of the system through the orifice at a controlled rate dm/dt , which is equal to the multiple of volume flow rate of water (dv/dt) into the core and drug concentration C_S .

$$\frac{dm}{dt} = \left(\frac{dv}{dt} \right) C_S$$

In principle, this delivery system dispenses drug continuously at a zero order rate until the concentration of the osmotically active salt in the system decreases below saturation solubility, where upon a non-zero order release pattern results. Recently, controlled release oral osmotic pump of naproxen sodium (Ramakrishna and Mishra, 2001) and ibuprofen (Ozdemir and Sahin, 1997) have been developed.

Diltiazem hydrochloride (DLTZ) is a calcium channel blocker widely used for the treatment of angina pectoris, arrhythmia and hypertension. Its short biological half-life and thus frequent administration (usually three to four times a day) makes it a suitable candidate for controlled release and/or sustained release (CR/SR) preparations (Chaffman and Brogden, 1985). DLTZ is a freely water-soluble drug and the release rate of DLTZ from oral osmotic pumps is usually high. Controlled porosity osmotic pump of DLTZ was developed, in which solubility of drug was reduced by adding sodium chloride (1 M concentration) to the core (McClelland et al., 1991). Sodium chloride reduced the solubility of DLTZ significantly and a constant release rate of drug was achieved. Further, Zentner et al. (1991) prepared controlled porosity solubility and resin-modulated osmotic drug delivery systems for the release of DLTZ. Hydrophilic polymers (HPs) are frequently added to the core to form polymer matrix. HPs can also be used (at lower to moderate concentration) to retard the release rate of highly water-soluble drugs from oral osmotic pumps to get desired zero order release rate. The designing essentially involves a mechanism, wherein the HPs control the release by producing hydrogel within the core which may restrict and delay the solvent contact with drug molecules and may increase the diffusional path length of solvent.

The objective of the present study was to investigate the effect of appropriate HPs on the release of DLTZ

from elementary osmotic pump. The drug:HP ratio was optimized on the basis of release rate of DLTZ. The mechanism and kinetics of drug release from the optimized formulations was established by fitting drug release data into different dissolution models.

2. Materials and methods

2.1. Materials

DLTZ was a gift sample from USV (P) Ltd., Mumbai, India. Cellulose acetate (320 S) was obtained from Sun Pharmaceutical Advanced Research Centre, Mumbai, India (manufactured by FMC Corp., USA). Hydroxy propyl methyl cellulose (HPMC, 200–300 cps, medium viscosity grade), polyethylene glycol (PEG) 400 and polyvinyl pyrrolidone (PVP K-25) were purchased from Himedia, India. Sodium carboxy methyl cellulose (NaCMC, medium viscosity 400–800 cps) and mannitol were procured from Loba Chemie, India.

2.2. Methods

2.2.1. Drug analysis

DLTZ was analyzed by ultraviolet (UV) spectrophotometric method at λ_{\max} 237 nm (Sood and Panchagnula, 1998). Calibration curves were prepared in distilled water, simulated gastric fluid (SGF pH 1.2) and simulated intestinal fluid (SIF pH 7.4) in the concentration range of 2–20 $\mu\text{g/ml}$ (Shimadzu 1601 UV/visible spectrophotometer). No enzymes were added to both SGF (pH 1.2) and SIF (pH 7.4). Correlation coefficients were found to be $r > 0.9994$ for all media and no interference of additives used in formulation was observed.

2.2.2. Formulation design

To optimize the content of HPs various formulations of DLTZ (coded as DIL 1–10) containing HPMC and NaCMC mixture (1:1 ratio and 5, 10, 15, ..., 50% w/w of drug) were prepared and the dose of DLTZ was kept constant (100 mg, i.e. thrice of conventional dose 30 mg with excess of 10 mg). Total weight of each core tablet was 350 mg and mannitol (also having osmogenic properties) was used as diluent. Mannitol content varied with varying amount of HP. Apart from

these, a plain formulation, which contained only DLTZ and mannitol (DIL P) was prepared for comparison study.

2.2.3. Granulation and punching

The granules were prepared by wet granulation method by using isopropyl alcohol as granulating solvent. PVP K-25 (25% w/w of drug) was used as a binder. Appropriate concentration of magnesium stearate and talc were added as lubricant and glidant, respectively. The granules were punched by an automated single punching machine (CIP machineries, Ahmedabad and Bro-Shell Remedies, Sagar, India) with concave punches (diameter, 10 mm). The punched tablets were of $7.4 \pm 0.22 \text{ kg/cm}^2$ average hardness. The drug content of the tablets was found to be within the limits of 95–105%.

2.2.4. Coating and drilling of the formulations

5% (w/v) coating solution of cellulose acetate (320S) polymer for casting semipermeable membrane and polyethylene glycol 400 (15% w/w based on polymer weight) as plasticizer in solvents, methylene chloride and methanol (80:20 ratio) (Ayer and Theeuwes, 1980, 1981; Zaffaroni et al., 1978) was used as an optimized formula. The coating was carried out by spray pan coating machine with hot air blower (Rowland chem. and machineries, Hyderabad, India). Pan was made up of stainless steel, having diameter of 22 cm and rotating speed of 25 rpm. The spray rate was fixed at 4 ml/min. Coated tablets were dried at 50 °C for 12 h. After coating, the formulations were evaluated for the percent weight increase. An orifice was mechanically drilled in the center of each pump. The aperture diameter and coating thickness were measured microscopically using empty shells obtained after complete dissolution of the contents (Table 1).

Table 1
Coating evaluation data of the formulations ($n = 5$)

Formulation	Average percentage weight increase (%)	Average coating thickness (μm)	Average aperture diameter (μm)
DIL 3	14.71 ± 0.96	600 ± 19	605 ± 7
DIL 5	14.3 ± 0.73	595 ± 23	612 ± 12
DIL P	14.46 ± 0.42	593 ± 15	598 ± 9

Table 2
Composition of optimized formulations

Ingredients	Quantity (mg)	
	DIL 3	DIL 5
Diltiazem hydrochloride	100	100
HPMC and NaCMC mixture (1:1)	15	25
PVP	25	25
Magnesium stearate	6	6
Talc	6	6
Mannitol	198	188

2.2.5. In vitro drug release

In vitro drug release of the formulations was conducted by using USP paddle type apparatus (rotation speed of 100 rpm and at 37 ± 1 °C). The dissolution medium was SGF (pH 1.2; 1000 ml) for first 2 h and SIF (pH 7.4; 1000 ml) for subsequent hours (Theeuwes et al., 1982). The samples were withdrawn at intervals of 1 h and analyzed immediately by UV spectroscopic method. The amount of DLTZ released was determined by measuring the absorbance at 237 nm.

According to the in vitro release profiles the formulations were optimized. Two formulations (DIL 3 and DIL 5, Table 2) that gave the desired release profile (near zero order) were selected for further characterization along with formulation that did not contain any polymer (DIL P). Formulation DIL 4 was not studied further for it exhibited almost similar release rate and profile as was recorded in the case of DIL 5. Minor changes in basic formula were incorporated for the preparation of optimized formulations.

2.2.6. Determination of theoretical release rate of DLTZ

The solubility of DLTZ at room temperature in the presence of potassium bicarbonate was determined. Excess amount of each material was added to the media in glass vials, the vials were capped tightly and

equilibrated at room temperature for 24 h. Aliquots of the resulting solutions were withdrawn from the vials and filtered. The DLTZ content was determined by UV analysis after appropriate dilution. The solubility of DLTZ in distilled water, SGF (pH 1.2) and SIF (pH 7.4) were found to be 611.16 ± 2.96 mg/ml, 636.63 ± 3.41 mg/ml and 606.38 ± 1.68 mg/ml, respectively.

Zero order release rate of the drug $(dm/dt)_z$ from an elementary osmotic pump, assuming a negligible osmotic pressure of the environmental fluid, is given by (Theeuwes et al., 1982),

$$Z = \left(\frac{dm}{dt} \right)_z = \frac{kA\pi_r S_d}{h}$$

where S_d is solubility of the agent inside the system (621.21 mg/ml), π_r is the total osmotic pressure of system, A is the surface area of the system (2.59 cm^2); k is the membrane permeability ($1 \times 10^{-5} \text{ cm}^3 \text{ cm/cm}^2 \text{ h atm}$), and h is membrane thickness. π_r and h values are shown in Table 3.

The osmotic pressure of the system can be calculated from equation (Martin et al., 1994),

$$\pi v = nRT, \quad \text{where, } \frac{n}{v} = C$$

Therefore $\pi = CRT$,

where π is the osmotic pressure, C is the molar concentration of drug inside the system, R is the gas constant, T is the absolute temperature, n is the number of moles of drug and v is the volume of system. The calculated values are recorded in Table 3.

2.2.7. Release models and kinetics

Generally the release of drug from oral osmotic systems is controlled by various factors such as osmotic pressure, aperture diameter, coating thickness, permeability of membrane, solubility of drug, etc. The in vitro release from system DIL P (which did

not contain any polymer) was very fast, and $t_{80\%}$ was determined to be 2 h. But, the release from other formulations (containing polymers) was comparatively more controlled, where $t_{80\%}$ was found to be more than 10 h. The findings led to a conclusion that retardance in release was due to the addition of HPs, therefore, it is necessary to find the kinetics in order to elucidate the mechanism of drug release from the systems containing HPs.

In order to describe the kinetics of drug release from controlled release preparations various mathematical equations have been proposed. The zero order rate Eq. (1) describes the systems, where the drug release is independent of its concentration (Najib and Suleiman, 1985). The first order equation Eq. (2) describes the release from systems, where release rate is concentration dependent (Desai et al., 1966). According to Higuchi model Eq. (3), the drug release from insoluble matrix is directly proportional to square root of time and is based on Fickian diffusion (Higuchi, 1963). The Hixson–Crowell cube root law Eq. (4) describes the release from the systems, where it depends on the change in surface area and diameter of the particles or tablets with time and mainly applies in case of system, which dissolute or erode over time (Hixson and Crowell, 1931; Abdou, 1989).

$$Q_t = k_0 t \quad (1)$$

$$\ln Q_t = \ln Q_0 - k_1 t \quad (2)$$

$$Q_t = k_H t^{1/2} \quad (3)$$

$$Q_0^{1/3} - Q_t^{1/3} = k_{HC} t \quad (4)$$

where Q_t is the amount of drug release in time t , Q_0 is the initial amount of the drug in tablet and k_0 , k_1 , k_H and k_{HC} are release rate constants for zero order, first order, Higuchi model and Hixson–Crowell rate equations, respectively.

In order to define a model, which will represent a better fit for the formulations, dissolution data can be further analyzed by Peppas and Korsenmayer equation Eq. (5) (Korsenmeyer et al., 1983; Ritger and Peppas, 1987a,b).

$$\frac{M_t}{M_\alpha} = kt^n \quad (5)$$

where M_t is the amount of drug released at time t and M_α is the amount released at time α (18 h), thus M_t/M_α

Table 3

The variables and theoretical release rate of DLTZ pumps

Formulations	Osmotic pressure (atm)	Coating thickness (μm)	Theoretical release rate (mg/h)
DIL 3	144.35	600	66.58
DIL 5	126.11	595	58.57
DIL P	169.48	593	83.49

is the fraction of drug released at time t , k is kinetic constant and n is diffusional co-efficient. The exponent ' n ' value can be used to characterize the mechanism of drug release (Peppas, 1985; Schwartz et al., 1968).

Drug release data obtained was applied to different drug release models in order to establish the drug release mechanism and kinetics. Criteria for selecting the most appropriate model was based on best goodness of fit and smallest sum of squared residuals (Parab et al., 1986).

3. Results and discussion

3.1. Formulation optimization

According to the in vitro release profile obtained, two optimized formulations of DLTZ (DIL 3 and DIL 5, Table 2) were further prepared. Punching, coating and drilling were carried out. Coating evaluation confirmed uniform thickness of film and the uniformity of aperture diameter (Table 1). In vitro drug release was determined and was reproducible. The prepared formulations were working well with total intactness of semipermeable membrane during the dissolution. In case of formulation DIL 5 negligible swelling of the system was observed, which might be due to higher content of HP. The empty shells obtained after 24 h of dissolution were left out with nearly 5% of drug inside. The empty shells were semitransparent, however, absolutely intact during the course of dissolution.

3.2. In vitro drug release

The formulation DIL P, which did not contain polymer, however, showed burst release where 90% of the drug was released within 2 h. It was further confirmed by $t_{80\%}$ values (time to release 80% of the drug content, Fig. 1). Formulation DIL 5 showed comparatively slower release rate than formulation DIL 3 probably due to higher content of hydrophilic polymer. Both the formulations showed no burst release and gave satisfactory controlled release. The curve between percent cumulative drug release and time confirmed that almost 80–90% of the drug released in 18 h (Fig. 1). The average release rates of the formulations for first 10 h were calculated. They were 6.88 ± 1.5 mg/h and 5.97 ± 1.3 mg/h for DIL 3 and DIL 5, respectively. The release rate was almost constant up to a time period of 10–12 h followed by gradual decrease in the release rate with decreasing osmotic pressure of the system (Fig. 2).

3.3. Effect of hydrophilic polymers on the release

The $t_{80\%}$ values determined from percent cumulative drug release versus time plots and release rate diagrams confirmed the effect of hydrophilic polymer on the release of DLTZ from the pumps (Figs. 1 and 2). Formulation DIL 5 showed slower release compared to DIL 3 and both the formulations gave relatively slower release rate than formulation DIL P that devoid of any polymer. The comparison of theoretical release rate with actually determined in vitro release rate also

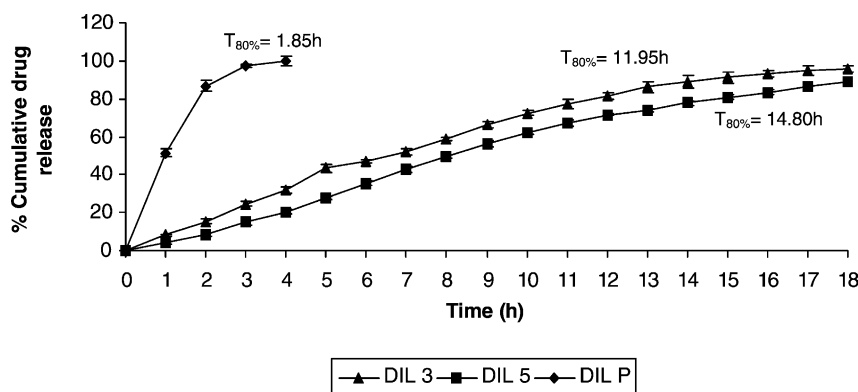


Fig. 1. In vitro cumulative release of DLTZ from optimized formulations.

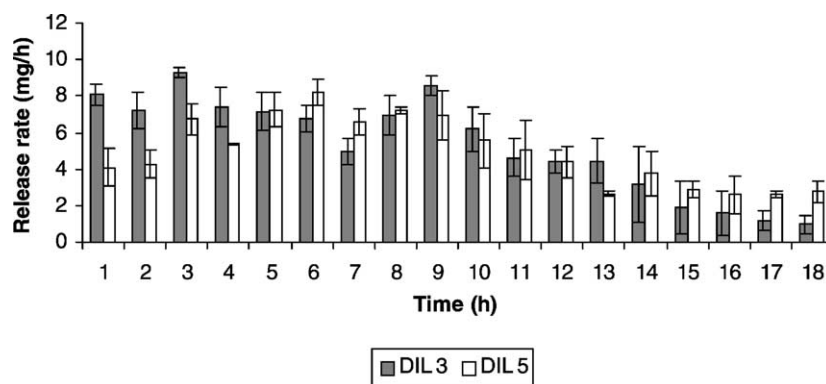


Fig. 2. In vitro release rate of DLTZ from optimized formulations.

confirmed the role of HPs in the slower and controlled release. The results suggest that appropriate addition of release retardants especially HPs can successfully control the release of highly water-soluble drugs from the elementary osmotic pumps.

3.4. Drug release kinetics

The linear nature of the plots between percent cumulative drug release and time suggests that none of the formulations follow first order kinetics, which is confirmed by the higher sum of squared residuals and comparatively less correlation co-efficient (Table 4).

Table 4

Regression analysis and correlation co-efficient values for dissolution data of formulations according to various kinetic models

Kinetic models	Parameters	Formulations	
		DIL 3	DIL 5
Zero order	r	0.9785	0.9869
	SSQ	17844.9	16401.8
	k_0	5.48	5.29
First order	r	−0.9939	−0.9878
	SSQ	2147.7	2155.8
	k_1	−0.0555	−0.0795
Higuchi model	r	0.9796	0.9883
	SSQ	18465.5	15857.9
	k_H	5.58	5.21
Hixson–Crowell model	r	0.9982	0.9986
	SSQ	15.29	9.99
	k_{HC}	0.1773	0.1434

The linear nature of the curves obtained for zero order, Higuchi model and Hixson–Crowell model suggests that the release from the formulations may follow any one of these models (not shown). While considering the higher correlation co-efficient values and less sum of squared residual (SSQ) values (Table 4), the release data seem to better fit with Hixson–Crowell model. Zero order and Higuchi model, moreover show higher SSQ values and comparatively small correlation co-efficients. Applicability of the release curves to the Hixson–Crowell equation indicated a change in surface area and diameter of the particles with progressive dissolution of the matrix as a function of time. Also, the change in diffusional path length along with the change in surface area and diameter of the particles during dissolution process follows cube root law.

Based on Korsmeyer–Peppas Power model Eq. (5), drug release data further analyzed for curve fitting and the results (DIL 3: $n = 0.5477$, $r = 0.9894$ and $k = 1.836$, DIL 5: $n = 0.6726$, $r = 0.9913$ and $k = 0.614$) confirmed that the formulations followed non-Fickian diffusion kinetics (because $n > 0.5$).

4. Conclusion

From the results obtained, it can be inferred that the release of freely water-soluble drug DLTZ from elementary osmotic pump can be controlled efficiently by the addition of HPs in to the core formulations. The oral osmotic pumps possess many advantages over the simple matrix type of SR/CR oral dosage forms.

The pumps gave better controlled release and time duration for the release can be extended up to 24 h. This can lead to the development of these formulations as potential candidate for once a day dosage form. The kinetics of drug release from formulations follow Hixson–Crowell cube root model and mechanism of release would follow non-Fickian diffusion process. It can be concluded from the study that HPs can play a considerable role in controlling the release of DLTZ (or other highly water-soluble drugs) from elementary osmotic pumps.

Acknowledgements

Authors are thankful to Dr. Jayant Kargji, SPARC, Mumbai, India for providing cellulose acetate, to USV Ltd., Mumbai, India, for providing gift sample of DLTZ and to Mr. J.K. Jain, Bro-Shell Remedies, Sagar, India for providing machinaries. Fellowship from UGC and ICMR, New Delhi, India to D. Prabakaran is duly acknowledged.

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Investigations on the drug releasing mechanism from an asymmetric membrane-coated capsule with an in situ formed delivery orifice

Ying-Ku Lin, Hsiu-O Ho*

Graduate Institute of Pharmaceutical Sciences, Taipei Medical University, 250 Wu-Hsing Street, Taipei 110, Taiwan, ROC

Received 13 November 2002; accepted 10 January 2003

Abstract

Asymmetric membrane-coated capsules with in situ formation of a delivery orifice were examined for their improved osmotic effects. The release mechanisms were investigated for drugs with both moderate to high water solubility and those with poor water solubility. The capsule wall membrane was produced by a phase-inversion process, in which an asymmetric membrane was formed on stainless steel mold pins by dipping the mold pins into a coating solution containing a polymeric material followed by dipping into a quenching solution. In situ formation of a delivery orifice in the thin membrane was proven by visualization of a jet stream of chlorophyll being released from the capsule. The release mechanism for drugs with moderate to high water solubility was mainly controlled by the osmotic effect, which is a function of the drug's solubility. Permeability across the asymmetric membrane of the capsule was determined to be $4.28 \times 10^{-6} \text{ cm}^2/\text{h-atm}$ at 37°C for drugs with water solubilities in a moderate to high range. Accordingly, the poorly water-soluble drug, nifedipine, was unable to create enough of an osmotic effect to activate drug release. Solubilization either by the addition of the solubility enhancer, SLS, or by a solid dispersion with HPMC could increase the solubility of nifedipine to a sufficient extent to activate drug release. It was found that the suspending ability induced by the viscous nature of HPMC further interacted with SLS to synergistically increase the maximal percent release and the release rate of nifedipine. The osmotic effect of this suspension ability was proposed as the underlying mechanism responsible for the release of poorly water-soluble drugs, i.e. nifedipine, from this system.

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Keywords: Asymmetric membrane; Osmotic pressure; Cellulose acetate; Nifedipine; In situ formation

1. Introduction

It is known that pharmaceutical agents can be delivered in a controlled pattern over a long period by osmotic pressure. There has been increasing

interest in the development of osmotic devices over the past two decades. Designs of various types of osmotic pumps have been reported [1–3] and reviewed [4,5]. Osmotic tablets with an asymmetric membrane coating, which can achieve high water fluxes, have been described [6]. The asymmetric membrane capsule described [7,8] is also an example of a single-core osmotic delivery system consisting

*Corresponding author. Tel./fax: +886-2-2377-1942.

E-mail address: hsuoho@tmu.edu.tw (H.-O Ho).

of a drug-containing core surrounded by an asymmetric membrane. One of the advantages of the asymmetric membrane capsule is the higher rate of water influx, allowing the release of drugs with lower osmotic pressures or lower solubilities. In spite of this advantage, there are many instances where the solubility of a drug is too low to provide a reasonable driving force for water ingress. In such situations, various methods have been reported to enhance this driving force either by improving drug solubility, including the use of crystal habit modifiers [9], assisting with lyotropic crystals [10,11], adding pH-regulating excipients [12,13], complexing with inclusion compounds [14], or by enhancing the contact surface area of the drug by utilizing wicking agents [15].

In a majority of cases, osmotic delivery systems contain at least one delivery orifice in the membrane for drug release. Pre-formation and in situ formation are two possible ways of creating delivery orifices in membranes. Laser drilling is one of the most commonly used techniques to create preformed delivery orifices in osmotic tablets [16]. The use of modified punches for producing a preformed delivery orifice in osmotic dosage forms is also possible [17]. Controlled-porosity osmotic pumps (CPOP), contain water-soluble additives in the coating membrane, which after coming in contact with water, dissolve resulting in in situ formation of a microporous membrane [18–20]. The resulting membrane is substantially permeable to both water and dissolved solutes. Because of that, the mechanism of drug release from these systems was found to be primarily osmotic, with simple diffusion to a minor extent. Systems with passageways formed in situ are also described in US patent no. 5,736,159 [21]. A small opening is formed at the edge of the tablet caused by the expansion of expandable material in the core.

The size of the delivery orifice must be optimized in order to control the amount and rate of drug released from osmotic systems. Preformed delivery orifices would be advantageous for the design of delivery orifices and hence the ability to control drug release. However, a complicated continuous process such as laser drilling, or specially designed machinery such as modified punches would be required for commercial production scale. Therefore, in situ formation of delivery orifices in the semipermeable

membrane of osmotic systems would be less burdensome for commercial production. Although it is known that delivery orifices can be created in situ in semipermeable membranes, it is still necessary to utilize expanding material in the core of or added pore formers in the membrane. Since asymmetric membranes in osmotic membranes consist of a very thin, dense skin structure supported by a thicker, porous structural layer, in situ formation of delivery orifices on this thin layer is potentially possible with no assistance. In this study, we explored whether delivery orifices could be formed in situ on asymmetrically coated membranes. Compliance with an osmotic control mechanism of drug release and the influential factors were investigated.

2. Experimental section

2.1. Materials

Cellulose acetate (CA 398-10) was supplied by Eastman Chemicals Co. (Kingsport, USA). Nifedipine (NF) and felodipine (FL) were provided by Merck (Darmstadt, Germany) and the Sigma Chemical Co. (St Louis, MO, USA), respectively. As nifedipine was light sensitive, all samples were kept in an amber-colored container, wrapped in aluminum foil, or covered by a blanket during the whole experimental process. Chlorpheniramine maleate, pyridoxine, theophylline, chlorophyllin, glycerin, Tween 80, sodium lauryl sulfate (SLS) were from the Sigma Chemical Co. (St Louis, MO, USA). Triethyl citrate (TEC), acetonitrile, methanol were from Merck (Germany). Hydroxypropylmethylcellulose (HPMC, 5 cps, 15 cps and 50 cps) was purchased from the Shin-Etsu Chemical Co. (Japan).

2.2. Methods

2.2.1. Capsule preparation

Capsules with asymmetric membranes were produced using a dip-coating process. The stainless steel mold pins were dipped into polymer solutions consisting of 15% w/v cellulose acetate (CA 398-10, Eastman Fine Chemical) dissolved in a mixture of acetone/alcohol/glycerin (62 ml/34.5 ml/10 g), followed by quenching in an aqueous solution (10%

w/v glycerin). After quenching, the pins were withdrawn and allowed to air-dry. Then, the capsules were stripped off the pins, trimmed to size, and kept in desiccators until use.

2.2.2. Osmotic pump capsule preparation

Asymmetric membrane capsules were fabricated and filled with the desired amount of drug or drug–excipient mixture by hand. Physical mixtures of nifedipine were prepared simply by mixing nifedipine and sodium lauryl sulfate with hand shaking in a plastic bag for at least 15 min. A solvent method was employed to prepare solid dispersion systems for nifedipine. HPMC were selected as the water-soluble polymers. After dissolving nifedipine and HPMC in a suitable volume of an acetone/water mixture, the solvent mixture was completely evaporated in a forced-air convection oven at a temperature of 50–60 °C. Dried residues were ground with a coffee mill, and granules passing an 80-mesh sieve were collected. These solid dispersion samples were then stored in desiccators protected from light until use. After the filling operation, the capsules were capped and sealed with a sealing solution, which contains 16% cellulose acetate in a mixture of acetone/alcohol (62 ml/34.5 ml).

2.2.3. Solubility tests

Excess drugs were suspended in deionized water and maintained at 37 °C for at least 72 h with intermittent shaking. Immediately after filtration from the syringe, filtrate in the middle portion was sampled and properly diluted. The drug concentration was assayed with a validated method to determine the solubility in deionized water at 37 °C.

2.2.4. Release test

An in vitro dissolution test was performed using USP dissolution methodology (Apparatus 2, 50 rpm, 37 °C, 500–1000 ml of medium with sinker) (JASCO, Model DT-610). In all cases, an appropriate volume of sample was withdrawn at pre-determined time intervals and assayed by either a validated UV absorbance measurement or by an HPLC/UV method (Helios, Unicam and Dynamax, Rainin Instrument).

2.2.5. HPLC analysis

The HPLC system consisted of a Rainin solvent delivery pump (Dynamax, model SD-200), a UV detector (Dynamax, model UV-1), an automatic sample injector (Dynamax, model AI-3), and an SISC for data analysis. The UV detector wavelength was set at 350 nm for nifedipine. Separation was achieved using an Inertsil column (C₁₈, 5×250 mm). The mobile phase consisted of water and acetonitrile in a ratio of 3:7 (v/v). A flow-rate of 0.8 ml/min was used.

2.3. Theoretical considerations

For drug delivery systems that release a drug by osmotic pressure, the volumetric flux of water from the surrounding aqueous medium into the device core is given by:

$$\frac{dV}{dt} = \frac{A}{h} L_p \sigma \Delta \pi \quad (1)$$

where dV/dt is the volumetric influx rate of water into the device core, A is the surface area of the capsule, h is the wall thickness, L_p is the filtration coefficient, σ is the reflection coefficient, and $\Delta \pi$ is the osmotic pressure difference across the wall. The zero-order release rate during the initial portion of the release profile is given by:

$$\frac{dM}{dt} = \frac{dV}{dt} S \quad (2)$$

where dM/dt is the release rate, dV/dt is given by Eq. (1), and S is the concentration of the component in the fluid being pumped. If the capsule contains only one component, the osmotic pressure difference is caused by a saturated solution of the component on one side of the capsule wall and sink conditions (assumed) outside the capsule walls. Also, assuming ideality, the expression for $\Delta \pi$ can be written as:

$$\Delta \pi = MRT = \frac{S}{M.W.} RT \quad (3)$$

where R is the universal gas constant, T is the temperature, $M.W.$ is molecular weight, and S is the saturation solubility of the single component (drug). Substituting for $\Delta \pi$ into Eq. (1) and substituting the resultant expression for dV/dt into Eq. (2), the following relation is obtained:

$$\frac{dM}{dt} = \left(\frac{A}{h} L_p \sigma RT \right) \frac{S^2}{M.W.} \quad (4)$$

Eq. (4) indicates that a plot of the release rate versus ($S^2/M.W.$) should be linear with a slope given by the expression in parentheses. Based on Eq. (4), the water permeability (L_p) of the asymmetric membrane capsule wall was calculated.

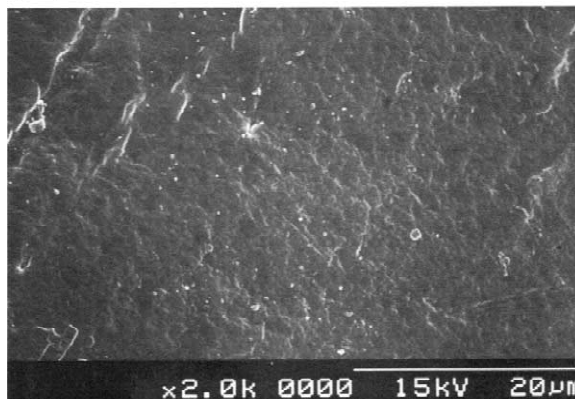
3. Results and discussion

The asymmetric membrane-coated capsules prepared appeared to be white, opaque, and glossy with no visible imperfections. Weight variations in the asymmetric membrane capsules and their dimensions were demonstrated to be consistent with little variation. This confirms that the process of producing these capsules is reproducible. Scanning electron micrographs (SEMs) of the capsule walls show that the membrane was asymmetric with a relatively thin dense region on a porous substrate with longer micropores (Fig. 1). No pore structures were shown in the dense region (Fig. 1A). The porous region at both $\times 100$ (Fig. 1B) and $\times 200$ magnification (Fig. 1C) reveals numerous pore structures.

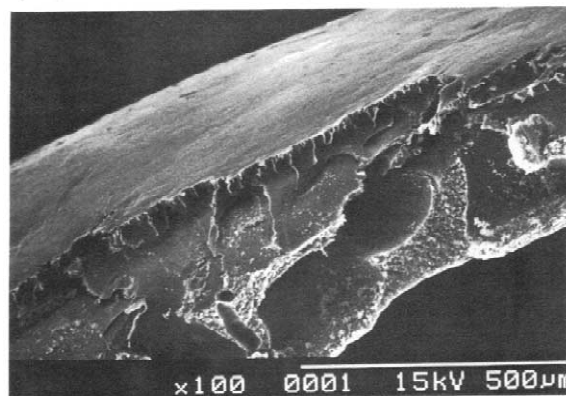
In situ formation of a delivery orifice for releasing drug was proven with photographs as shown in Fig. 2 in which a deeply colored jet stream of chlorophyll from an open hole can be observed when an asymmetric membrane-coated capsule encapsulated with chlorophyll was suspended in the water medium. This delivery process continued for another 30 min as demonstrated by Fig. 2B. However, when this capsule was suspended in a 5% NaCl solution, the osmotic effect was inactivated, and no release of chlorophyll (Fig. 2C) was observed. This indicates that in situ formation of a delivery orifice is possible in the thin structure of the asymmetric membrane. The osmotic pressure created might play an important role in the switching on or off of this mechanism.

The osmotically controlled drug release mechanism from asymmetric membrane-coated capsules was further characterized based on Eq. (4) using drugs of varying solubilities. The core formulation consisted of drug alone but with varying solubilities

(A)



(B)



(C)

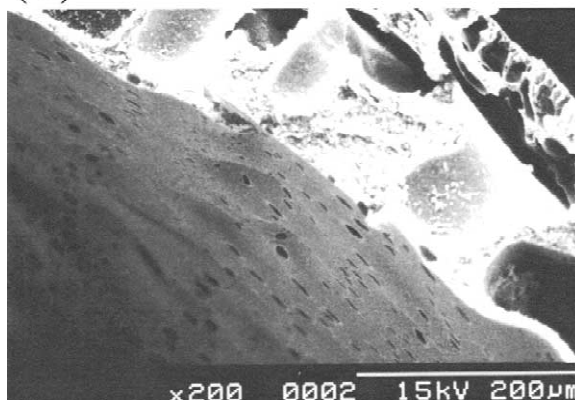


Fig. 1. Scanning electron micrographs of asymmetric membrane capsule wall at formulation A (A) dense region (outer layer) at $\times 2000$ magnification, (B) cross-section at $\times 100$ magnification, (C) porous region (inner layer) at $\times 200$ magnification.

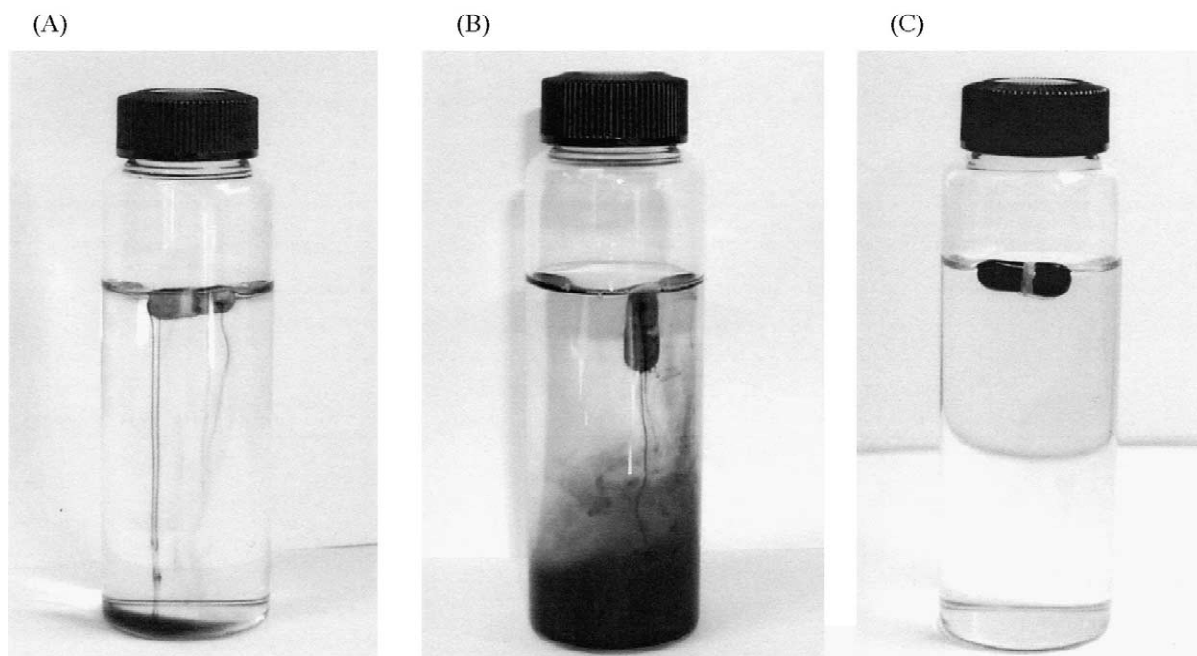


Fig. 2. Photograph of asymmetric membrane capsule with chlorophyllin in water. (A) After 30 min, (B) After 90 min, (C) In NaCl 5% solution.

in water (chlorpheniramine maleate, pyridoxine, theophylline, felodipine, and nifedipine); these were individually loaded into the asymmetric membrane

capsule. The in vitro drug release profiles from asymmetric membrane capsules are shown in Fig. 3. The initial portion of the drugs release profiles were

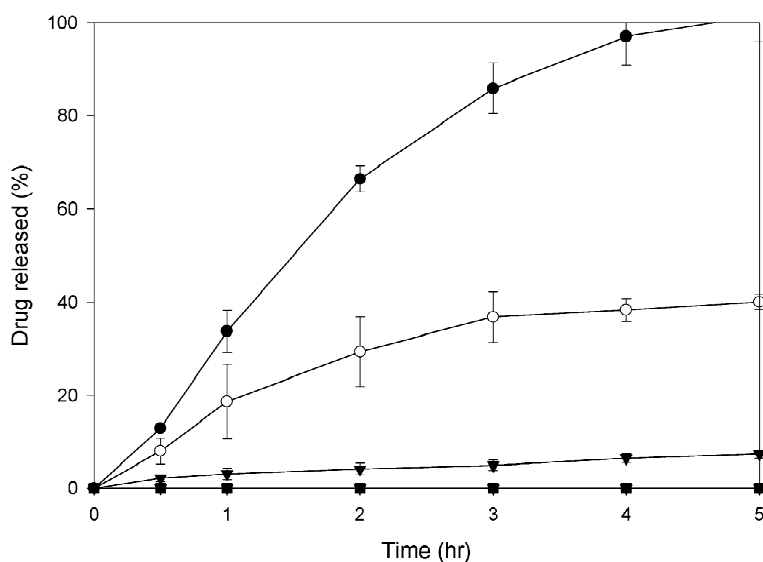


Fig. 3. Release profiles of drugs from asymmetric membrane capsule (formulation A) in water (50 rpm, $n=3$). Key: (●) Chlorpheniramine maleate 50 mg; (○) pyridoxine 50 mg; (▼) theophylline 50 mg; (▽) felodipine 50 mg; (■) nifedipine 50 mg.

Table 1

The solubility of drugs in water at 37 °C ($n=3$)

Drug	<i>M.W.</i>	<i>S</i> (mg/ml)	$S^2/M.W.$	Release rate (%/h)	Release rate (mg/h)
Chlorpheniramine maleate	390	576.72 ± 16.24	852.84	33.90	16.95
Pyridoxine	205	224.47 ± 0.96	245.79	12.58	6.29
Theophylline	180	7.18 ± 0.03	0.29	1.30	0.65
Felodipine	384	<1	~0	~0	~0
Nifedipine	346	<1	~0	~0	~0

used to calculate the initial drug release rate. The results in Fig. 3 reveal that both the amount released and the release rate were a function of drug solubility. In comparison with the drug solubilities listed in Table 1, the amount released was larger and the drug release rate was faster as drug solubility increased.

The graph displayed in Fig. 4 plots the release rate (dM/dt) versus the ratio of the square of drug solubility to molecular weight ($S^2/M.W.$) based on Eq. (4). A linear correlation between the initial drug release rate (calculated from the slope of the drug release profile) and $S^2/M.W.$ was observed. The slope of linear portion is $0.0185 \text{ cm h}^{-1} \text{ M}^{-1}$. By keeping all other factors constant, the drug release rate in the

initial portion of the profiles increased linearly with respect to the square of the drug solubility divided by the molecular weight of the corresponding drug as predicted by Eq. (4). A statistically significant correlation of $r^2=0.9936$ was demonstrated. This complies with the drug released by an osmotic pumping mechanism. Assuming ideality, where R is the Universal Gas Constant and T is the absolute temperature, L_p (at 37 °C) is calculated to be $4.28 \times 10^{-6} \text{ cm}^2/\text{h-atm}$ based on Eq. (4) with known values of $h=0.02 \text{ cm}$ and $A=3.4 \text{ cm}^2$. This value is comparable to that from a similar membrane design reported in the literature [8].

As concluded for asymmetric membrane-coated capsules with an in situ formed delivery system, the

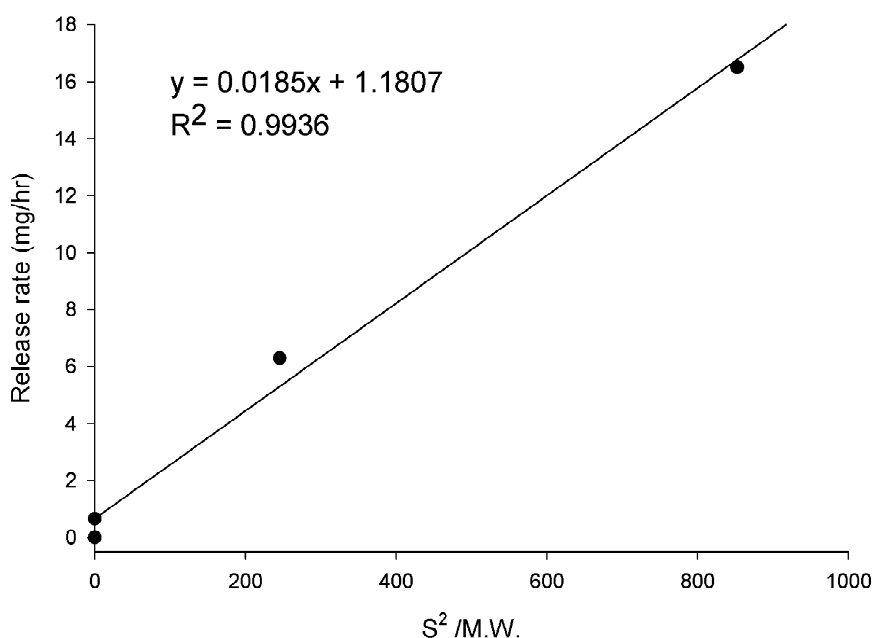


Fig. 4. Linear relationship between the release rate and the square of solubility divided by molecular weight of the drug.

osmotic effect is the main activation force for drug release. Similarly, drug solubility is expected to be the determining factor for the success of engineering asymmetric membrane-coated capsules with an in situ formed delivery orifice with a desirable release rate. It is likely that a drug with low solubility would not create enough osmotic pressure to activate drug release. Because of this, the drug release mechanism from an asymmetric membrane-coated capsule with in situ formation of a delivery orifice was further studied by examining the influence of core formulation variables including the added amount and viscosity of hydroxypropylmethylcellulose (HPMC) and the amount of sodium lauryl sulfate (SLS). Nifedipine was selected as a model drug because it has poor water solubility. All subsequent release studies were done in water medium with the addition of 1% Tween 80 as the solubilizing agent.

Fig. 5 shows that the amount of SLS in the core formulation had a marked influence on nifedipine release. When the added amount of SLS was at a 1:1 ratio to the nifedipine amount, only 2% of the nifedipine was released, whereas the release amount of nifedipine increased to 40% by adding SLS at a 20:1 ratio to the nifedipine amount. The release rate

Table 2

The solubility of nifedipine in SLS solution at 37 °C ($n=3$)

SLS concentration (w/v%)	Solubility (mg/ml)	S.D.
0.1	0.021	0.0002
0.5	0.166	0.0028
1.0	0.371	0.0063
2.5	0.799	0.0092
5.0	1.362	0.0099
10.0	2.296	0.0104
20.0	3.280	0.0425

apparently increased with the increased amount of added SLS. Possibly, the greater the amount of SLS is which is incorporated into the capsule, the larger the osmotic effects will be which can be activated to cause a greater amount of nifedipine to be dissolved and released. The osmotic effects of SLS on the release rate and the released amount of nifedipine could be attributed to two factors. One is the solubilization effect of SLS (Table 2) in enhancing the dissolved amount of nifedipine in the core medium for increasing the osmotic effect, and the other is that the dissolved SLS acts as an osmotic agent to increase the osmotic effect. Since SLS was

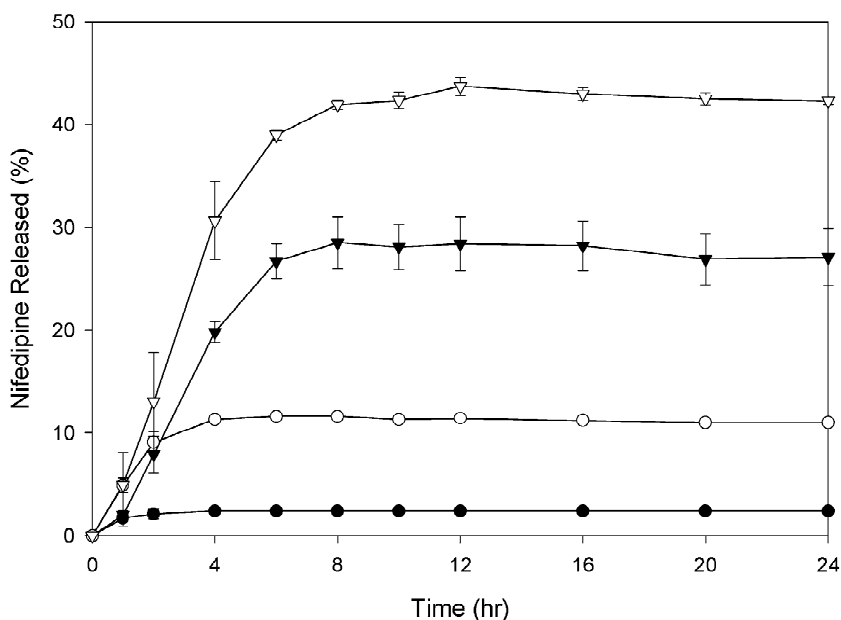


Fig. 5. Release profiles of nifedipine from asymmetric membrane capsule in 1% Tween 80 solution (50 rpm, $n=3$). Nifedipine (NF) was made by physically mixed method with SLS (S). NF/S ratio: (●) 1/1, (○) 1/5, (▼) 1/10, (▽) 1/20.

released through the in situ formed delivery orifice, it was released in company with nifedipine. When the SLS was exhausted, both mechanisms ceased, which terminated the release of nifedipine from these capsules. This leads to the released amount of nifedipine being proportional to the added amount of SLS. This quantitative relationship is illustrated in Fig. 6 by plotting the maximal percent released versus the ratio of SLS to nifedipine. The slope (2.196) of the linear plot can be used to predict what added amount of SLS per unit amount of nifedipine would be necessary to reach a maximal 100% release of nifedipine from this capsule system. Based on this, quite a large amount (about 440 mg) of SLS was possibly needed to completely release 10 mg nifedipine from this type of capsule by extrapolation. An in vitro dissolution test of nifedipine mixed with sodium lauryl sulfate at a weight ratio of 1:44 had been performed. It was fairly confirmed that the extent of drug release from this formulation was increased to about 85%. The result shown is closely consistent with the extrapolated prediction.

Fig. 7 illustrates the effect of viscosity grades of HPMC at the same level on the release pattern of nifedipine from these osmotic capsules with an in situ formed delivery orifice. Nifedipine was incorporated with HPMC in a solid dispersion form prepared

by the solvent method and then physically mixed with SLS. Compared with the core formulation which only contains nifedipine and SLS at a ratio of 1:10, the addition of HPMC of varying viscosities further increased both the release rate and the released amount of nifedipine. At the same level of HPMC, an increase in the released percentage of 60% was shown for HPMC with a viscosity of 5 cps, whereas increases to 70–80% were observed for HPMC with a viscosity of either 15 or 50 cps. The further promotion of the released amount of nifedipine by all viscosity grades of HPMC could be attributed to the enhancement of nifedipine solubility with the aid of the solid dispersion. However, this seems to indicate that the higher the viscosity of HPMC used, the larger amount of nifedipine which could be released and the faster the release rate which would result. Since the enhancement of nifedipine solubility using various grades of HPMC is comparable (Table 3), another mechanism seems to be operating to have such an influence.

Fig. 8 demonstrates the effect of different added amounts of HPMC of the same viscosity grade (50 cps) on the release pattern of nifedipine. The added amount of HPMC also had a pronounced influence on the release profile. Since an improvement in solubility of nifedipine using different ratios of

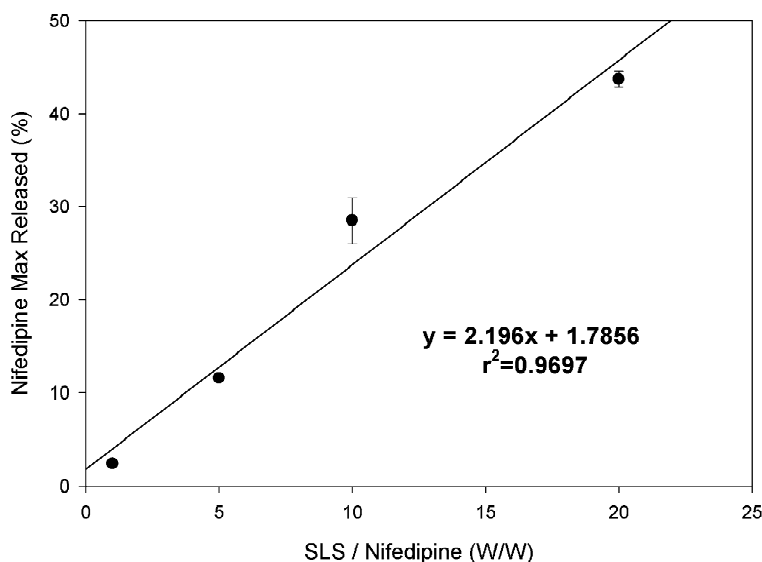


Fig. 6. Correlation of max released and SLS/nifedipine ratio.

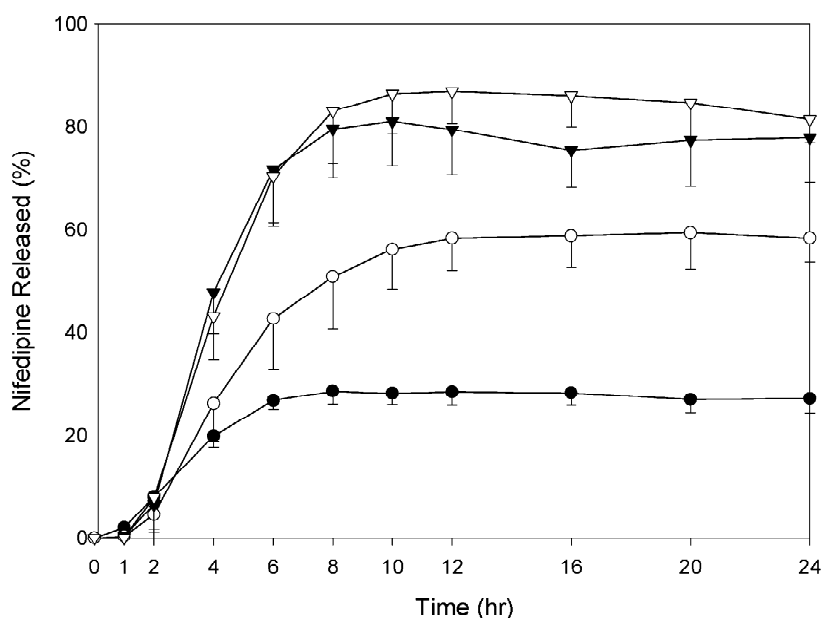


Fig. 7. Release profiles of nifedipine in 1% Tween 80 solution (50 rpm, $n=3$). Nifedipine (NF) was made by solvent method with HPMC and physically mixed with SLS (S). Key: (●) NF/S ratio: 1/10; (○) NF/HPMC 5 cps/S ratio: 1/10/10; (▼) NF/HPMC 15 cps/S ratio: 1/10/10; (▽) NF/HPMC 50 cps/S ratio: 1/10/10.

HPMC to nifedipine was not obvious, the role HPMC plays as a thickening agent in elevating the viscosity of the core suspension and, subsequently, preventing precipitation of nifedipine particles was suspected of possibly being the expression of a larger surface for dissolution. The larger the amount of HPMC used, the higher the viscosity of the core suspension would be, leading to the efficient suspension of nifedipine particles in the capsule. As a consequence, the release rate increased when increasing the added amount of HPMC by increasing the available surface area for dissolution. This mech-

anism seems capable of being explained by the effect of HPMC of varying viscosity grades. That is, a higher-viscosity HPMC would promote the more-efficient suspension of nifedipine particles for dissolution, leading to an increase in the released amount with an increase in the viscosity grade of HPMC used for preparing the solid dispersion.

Based on the above release profiles, we concluded that this asymmetric membrane-coated capsule with an in situ formed delivery orifice was able to release a water-insoluble drug such as nifedipine in the presence of an osmotic agent with the aid of a solubilizing agent and a suspension agent. Therefore, the system was operated by an osmotic-suspension co-controlled delivery mechanism somewhat different from either the generic EOP or the push-pull osmotic tablet. This proposed mechanism was further supported by the results demonstrated in Fig. 9.

Fig. 9A shows that the release of nifedipine was activated with a 1-h delay from the time the capsules were filled with the physical mixture of nifedipine and SLS at a ratio of 1:10. Two hours later, equilibrium had been reached with a release rate of about 0.5 mg/h, after which the release rate declined

Table 3

The solubility of various forms of nifedipine in water at 37 °C ($n=3$)

Formulation	Ratio	Solubility (mg/ml)
Nifedipine	—	0.011 ^a
Nifedipine/HPMC 5 cps	1:10	0.0422±0.0010
Nifedipine/HPMC 15 cps	1:10	0.0463±0.0021
Nifedipine/HPMC 50 cps	1:10	0.0439±0.0021
Nifedipine/mannitol	1:5	0.0132±0.0001
Nifedipine/mannitol	1:10	0.0104±0.0003

^a From Ref. [22].

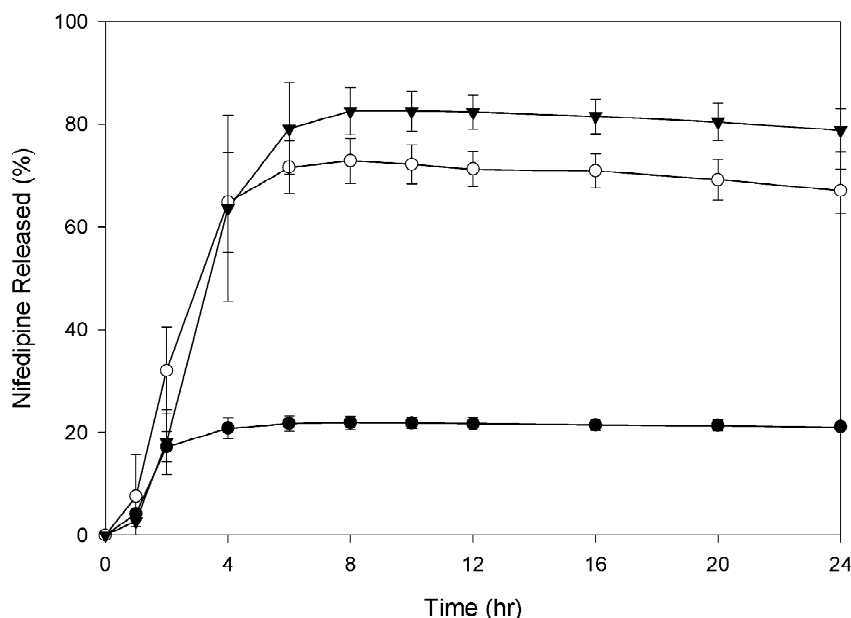


Fig. 8. Release profiles of nifedipine in 1% Tween 80 solution (50 rpm, $n=3$). Nifedipine (NF) was made by the solvent method with HPMC 50 cps (H) and physically mixed with SLS (S). NF/H/S ratio: (●) 1/1/10, (○) 1/5/10, (▼) 1/10/10.

4 h afterward, and the release of nifedipine had almost completely ceased by 10 h. In the presence of an osmotic agent such as SLS, water imbibed by the semi-permeable membrane into the capsule was gradually saturated with SLS to further build up the osmotic pressure difference between the internal system and the external environment. Simultaneously, the dissolved SLS caused the solubilization of nifedipine which was then available for release. During this period, the in situ formed delivery orifice might be created at the weakest point in the asymmetric membrane with an increase in osmotic pressure. It is expected that there is a lag time to reach such a state, which means that the release of drug is only activated with a 1-h lag time as shown in Fig. 9A for SLS. After that time, dissolved nifedipine and SLS were delivered through the orifice which had formed in situ. However, with the release of nifedipine at the expense of SLS, the osmotic effect gradually diminished and the solubilization effect was also retarded. This led to the release rate of nifedipine gradually decreasing with time. Then the release of nifedipine came to a complete stop when all the added amount of SLS was exhausted.

Nevertheless, Fig. 9A also shows that the release of nifedipine continued for more than 24 h with nifedipine in a solid dispersion form with HPMC. The release rate gradually reached its maximum at 8 h and was maintained at a plateau until 20 h. Compared to SLS, a longer period of release time but a lower release rate of nifedipine with HPMC was demonstrated. A longer period of release occurred because it takes time for all the HPMC to completely dissolve in such quiescent conditions inside the capsule, and the longer-sustained osmotic effect of HPMC might be a result of it being too large in size to be released. A lower release rate of nifedipine with HPMC might be attributed to a lower solubilization effect of HPMC which resulted in a reduced osmotic effect. However, maintaining a maximal release rate of 0.25 mg/h with a drug solubility of 43.9 $\mu\text{g/ml}$ (refer to Table 3) requires an osmotic pressure higher than 7.8×10^3 atm according to Eq. (4). The induction of osmotic pressure by the presence of HPMC was determined to be minimal (data not shown), since osmotic pressure is a colligative property that is determined by the molecular number, which would be less for such a polymer as HPMC with a high molecular weight.

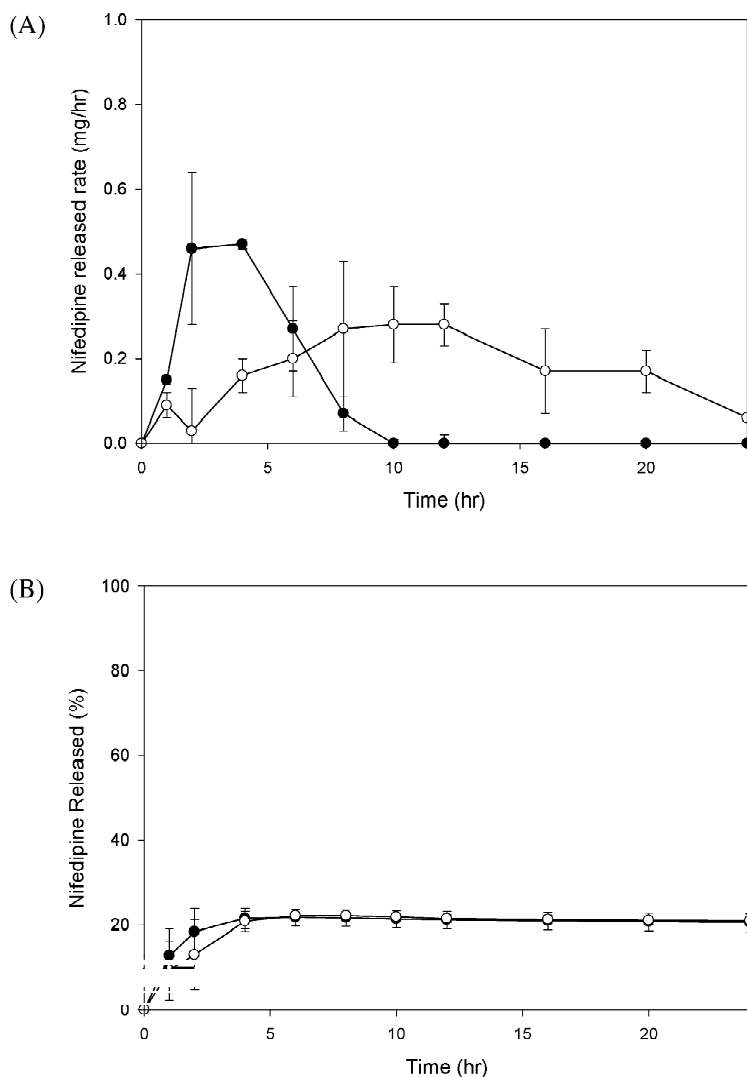


Fig. 9. Release rate of nifedipine from asymmetric membrane capsule in 1% Tween 80 solution (50 rpm, $n=3$). (A) Nifedipine (NF) was made by physically mixed with SLS (S) or solvent method with HPMC 50 cps (H). Key: (●) NF/S ratio: 1/10; (○) NF/H ratio: 1/10. (B) Nifedipine (NF) was made by the solvent method with mannitol (M) and physically mixed with SLS (S). NF/M/S ratio: (●) 1/10/10, (○) 1/5/10.

Therefore, the exact mechanism causing such a release rate with such a drug solubility was not due to the induction of a greater osmotic pressure. Because of that, with the same osmotic effect as in the case of SLS only, there must necessarily be a larger excess value in the solubility term than the real solubility to have such a large release rate and a cumulative released amount. This large excess value in the solubility term could be attributed to

nifedipine being released in both its insoluble and soluble forms, the latter of which stands for the exact solubility.

Fig. 9B further shows the release pattern of nifedipine from an encapsulated mixture consisting of a solid dispersion of nifedipine with mannitol prepared by the solvent method and physically mixed with SLS. A maximal amount of 20% was released for both mixtures, but with a faster rate for a larger

amount of mannitol. Mannitol is known for being an osmotic agent which should induce osmotic pressures proportional to its amounts which will synergize with the osmotic effect of SLS. This reveals that the higher osmotic effects induced by a larger amount of mannitol with the same amount of SLS does lead to an increase in the release rate, and it is maintained as it is until both are exhausted. Nevertheless, it is the solubility that determines the cumulative released amount of nifedipine during the active period of osmotic pressure as predicted by Eq. (4). Since the increase in nifedipine solubility with a two-fold increase in the amount of mannitol was insignificant as shown in Table 1, similarity in the maximal amount released is expected for both mixtures under a reasonable assumption that the active period of the osmotic effect for both cases did not significantly differ. The effect of solubility on the cumulative amount is predictable by Eq. (4). This means that only the soluble form of nifedipine was released from this formulation, which differs from both the insoluble and soluble forms of nifedipine being released from formulations containing HPMC.

We concluded that both insoluble and soluble forms of nifedipine were released from encapsulated formulations containing HPMC through the in situ formed delivery orifice, whereas only the soluble form of nifedipine was released from that containing mannitol. It is possible that HPMC acts as a thickening agent causing nifedipine particles to be suspended. During the experiment, water was imbibed creating a viscous suspension in situ inside the capsule, which resulted from the thickening agent (HPMC) and the imbibed water. Both the insoluble and soluble forms of nifedipine in the suspension were subsequently pumped out through the in situ formed delivery orifice. This explains why only the soluble form of nifedipine was released in formulations containing mannitol, which did not sufficiently increase the viscosity of the solution inside the capsule to suspend the insoluble form of nifedipine so it could be released. Therefore, drug release operated by both osmotic and suspension mechanisms. It should be pointed out that the sustainability of drug suspension caused by the thickening effect of the polymer was equally important as that of the osmotic action.

4. Conclusions

The in situ formed delivery orifice in controlled-release polymeric capsules with an asymmetric membrane wall is mainly responsible for the delivery of both soluble and poorly soluble drugs. In vitro release studies indicate that drug delivery from this asymmetric membrane-coated system is principally controlled by osmotic pressure for those drugs with moderate to high water solubilities. The asymmetric membrane-coated capsule prepared in this study has a permeability of $4.28 \times 10^{-6} \text{ cm}^2/\text{h-atm}$. This parameter can be used to predict the release rate of any drug encapsulated in this asymmetric membrane capsule. Solubilization of poorly water-soluble drugs with the incorporation of solubility enhancers is able to increase the release rate and the cumulative released amount. It was further found with solubilization in solid dispersions using a thickening agent such as HPMC, both insoluble and soluble forms of nifedipine were released as a result of the viscous solution induced by HPMC being able to suspend the insoluble form of nifedipine, rendering it available for release. This is not applicable for formulations containing an osmotic agent such as mannitol, which has no ability to induce the viscosity required to suspend nifedipine particles. Therefore, it was proposed that the mechanisms responsible for the release of nifedipine from this system were the simultaneous osmotic and suspension effects.

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patients with early RA may affect the risk of ischemic cerebrovascular events. The results must though be interpreted in its context, as the population of this study was relatively young and had a low frequency of traditional CV risk factors.

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Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2014-eular.2536

THU0142 SAFETY OF GLUCOCORTICOID FOR EARLY RHEUMATOID ARTHRITIS: A META-ANALYSIS OF RANDOMISED CONTROLLED TRIALS

S. Mitrovic¹, L. Fardet², C. Vatiér³, T. Barnetche¹, T. Schaevebeke¹, C. Gaujoux-Viala⁴. ¹Service de Rhumatologie, CHU de Bordeaux, Université Bordeaux Segalen, Bordeaux; ²Service de Médecine Interne, CHU St Antoine, Université Paris 6; ³Service de Nutrition, GH Pitié-Salpêtrière- UMR-S938, Université Paris 6, Paris; ⁴Rheumatology, Nîmes University Hospital, EA 2415, Université Montpellier I-Nîmes, Nîmes, France

Background: Several studies have shown structural and clinical benefit of corticotherapy (CT) for 1 to 2 years treatment of recent-onset rheumatoid arthritis (RA). However, because of its numerous adverse effects (AE), CT prescription is still under debate.

Objectives: The aim of this study is to evaluate the tolerance to CT for early RA. **Methods:** We carried out a systematic literature review on PubMed, EMBASE and Cochrane library until July 2013. The research was manually completed by the analysis of all references identified and of all abstracts presented at ACR and EULAR conferences of the past 2 years. All randomised placebo-controlled trials conducted on adult patients recently diagnosed (<3 years) with RA were selected. Data regarding AE, serious AE, arterial hypertension (HTN), diabetes, gastrointestinal AE, cephalgia, osteoporotic fractures and ophthalmic complications within 2 years of treatment were collected. Discontinuations due to treatment intolerance were also taken into account. Pooled Odds-Ratios were calculated by meta-analysis using the Mantel-Haenssen method. In case of significant heterogeneity, a random-effects model was used. Sensitivity analyses were based on the dose used (low-dose ≤10mg/day of equivalent prednisone and high-dose) and duration of treatment.

Results: Out of 1367 selected articles 16 were analysed. These were based on 12 randomised controlled trials involving a total of 2481 patients (mean age=54 years, 67% of women, mean of RA progression=5.3 months). Eight studies were based on low-dose CT and 4 on high-dose CT. A significant higher number of epigastralgia but not ulcers were reported in the CT group compared to placebo. No other significant difference could be observed in terms of AE (see table).

Criterion	Odds ratio [95% CI]
Adverse event	1.13 [0.80, 1.59]
Serious adverse events	0.94 [0.61, 1.45]
Discontinuation due to intolerance	1.36 [0.93, 1.98]
HTN	1.15 [0.72, 1.85]
Hyperglycemia	1.73 [0.75, 4.03]
Epigastralgia	1.76 [1.05, 2.95]
Osteoporotic fractures	1.46 [0.56, 3.79]

Conclusions: CT associated with background treatment is well tolerated in recent-onset RA, with only an increase of epigastralgia events in the first two years of treatment. Although patients included in clinical trials are selected and subject to long term AE, a low-dose may be recommended for early RA.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2014-eular.5481

THU0143 PHARMACOKINETICS, BIOAVAILABILITY AND SAFETY OF A MODIFIED RELEASE ONCE DAILY FORMULATION OF TOFACITINIB IN HEALTHY VOLUNTEERS

M. Lamba, R. Wang, T. Fletcher, C. Alvey, A. Hazra, J. Kushner, J. Larmann, T. Stock. *Pfizer Inc, Groton, United States*

Background: Tofacitinib is a novel, oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). The efficacy and safety of an immediate-release (IR) formulation of tofacitinib, dosed twice daily (BID), has been assessed in patients with active moderate to severe RA. To facilitate once daily (QD) dosing, a novel modified-release (MR) formulation has been designed to achieve comparability of key systemic exposure parameters.

Objectives: To compare the extent of exposure between a single dose of tofacitinib MR 11 mg vs an IR 2x5 mg dose in healthy volunteers (HV).

Methods: This was a randomised, open label, 2-way cross-over study conducted in 26 HV. Following an overnight fast, HV were randomised to receive either a single dose of MR 11 mg (MR; test) or IR 2 x 5 mg (IR; reference). Treatments were separated by a 72-hour (h) washout. Pharmacokinetic (PK) parameters were calculated using non-compartmental analyses. The primary endpoint was extent of tofacitinib exposure, measured as area under the concentration-time curve from time zero extrapolated to infinite time (AUC_{inf}). A mixed-effects model was used to

generate adjusted geometric mean ratios (MR/IR) and 90% confidence intervals (CIs). The steady-state (SS) profiles of tofacitinib MR and IR were predicted using single-dose data from this study.

Results: All 26 HV completed the study and were included in the analyses. The study population had a mean age of 33.6 years, a mean body weight of 77.5 kg, and was 19% female. For the MR and IR formulations, geometric mean AUC_{inf} (ng*h/mL) was 297.5 and 286.3, respectively, resulting in an MR/IR ratio of 103.91% (90% CI: 100.49%, 107.45%). Maximum plasma concentration (C_{max}; ng/mL) adjusted for formulation was 40.75 and 44.10 for MR and IR, respectively, resulting in an MR/IR ratio of 92.40% (90% CI: 84.99%, 100.45%). For both parameters, 90% CI values were wholly contained within the 80–125% range of bioequivalence. Mean terminal half-life was 5.71 h and 3.41 h for MR and IR formulations, respectively. The most common adverse events (AEs) were nausea, abdominal pain, back pain and headache. The incidence of AEs was similar between treatment groups and no serious AEs were reported. Predictions following SS dosing indicate similar time above JAK1/3 half maximal inhibitory concentration signalling thresholds and similar AUC, peak concentration and minimum concentration values between MR and IR formulations.

Conclusions: This study demonstrates the single dose equivalence of AUC_{inf} and C_{max} of the MR and IR formulations of tofacitinib. Single doses of both formulations were well tolerated. This novel MR formulation of tofacitinib facilitates an opportunity to enable QD dosing, while maintaining systemic drug concentrations similar to the IR formulation (administered BID). Multiple-dose studies will be conducted to confirm the predictions of the SS PK profile and demonstrate equivalence between formulations following SS dosing.

Acknowledgements: This study was sponsored by Pfizer Inc. Pfizer personnel were involved in protocol development and data analysis. Editorial support was provided by Claire Cridland of CMC and funded by Pfizer Inc.

Disclosure of Interest: M. Lamba Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, R. Wang Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, T. Fletcher Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, C. Alvey Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, A. Hazra Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, J. Kushner Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, J. Larmann Shareholder of: Pfizer Inc, Employee of: Pfizer Inc, T. Stock Shareholder of: Pfizer Inc, Employee of: Pfizer Inc

DOI: 10.1136/annrheumdis-2014-eular.1521

THU0144 THE INFLUENCE OF THE METHYLENETETRAHYDROFOLATE REDUCTASE (MTHFR) POLYMORPHISM ON METHOTREXATE TREATMENT OUTCOME IN PATIENTS WITH RHEUMATOID ARTHRITIS IN THE EAST BOHEMIAN REGION

T. Soukup¹, J. Někviňová², M. Dosedel³, P. Bradná¹, A. Kubena³, A.C. Fernandez³, T. Veleť¹, J. Vlček³, P. Pavěk³. ¹2nd Department of Internal Medicine-Gastroenterology, Charles University in Prague, Medical Faculty and University Hospital in Hradec Kralove; ²Institute of Clinical Biochemistry and Diagnostics, Charles University in Prague, University Hospital in Hradec Kralove; ³Faculty of Pharmacy in Hradec Kralove, Charles University in Prague, Hradec Kralove, Czech Republic

Background: Identifying genetic predictors of methotrexate (MTX) therapy response in patients with rheumatoid arthritis (RA) may have importance for clinical benefit optimization. MTX therapeutic effect is achieved by inhibiting enzymes of the folate and adenosine pathways. MTX response is mainly influenced by 5,10-methylenetetrahydrofolate reductase (MTHFR) enzyme activity.

Objectives: The aim of the study was to determine whether single nucleotide polymorphisms (SNPs) in the MTHFR gene are predictive of MTX response according to the change of DAS28 after a 6-month MTX treatment in RA patient cohort of the East Bohemian population. The two SNPs 677C>T (rs1801133) and 1298A>C (rs1801131) of the MTHFR gene have been genotyped.

Methods: Monocentric, regional, retrospective and prospective, cross-sectional study. The 118 patients (mean age 57 years, SD ±12.7, age of 27- 83 years, and 31 male – 26%) were enrolled in study, all of whom fulfilled the American College of Rheumatology (ACR) 1987 criteria, and currently or previously taking MTX oral treatment, either as monotherapy (n=16) or in combination with DMARDs or corticoids (n=102). The concomitant treatment were sulfasalazin (n=18), leflunomide (n=10), hydrochloroquin (n=18), cyclosporine (n=8), biologics (n=7) and glucocorticoids (n=86). Treatment outcome was evaluated using DAS28 score and based on EULAR criteria at the beginning of MTX treatment, prospectively at entry into study or retrospectively from patients' file (in case of patients with history of MTX treatment) and after a 6-month therapy. Genotyping assays: Leukocyte genomic DNA will be extracted from whole blood using a QIAamp DNA Blood Mini Kit (Quiagen). Genotyping was performed by qPCR allelic discrimination using commercial TaqMan (allele-specific) assays (LifeTechnologies) or sequencing. Statistical analysis was carried out in PASW[®] 18 software. Statistical dependences were tested by GLM (Generalized Linear Models), with bootstrap procedure.

Results: Results of the study thus show that higher dose of MTX lead to better response of DAS28, i.e. 1.19 DAS28/10mg MTX (p=0.02). In case of polymorphism 677C>T, mean response on MTX treatment (expressed by decrease of DAS 28 after a 6-months treatment) in CC homozygotes was found 1.59 DAS/10mg MTX (median of MTX dose); CI 95% = (0.12, 3.06); p=0.034, in CT heterozygotes 0.70 DAS28/10mg; CI 95% = (-0.82, 2.22); p=0.36, and in homozygotes TT 1.83 DAS 28/10mg; CI 95% = (-1.70, 5.37); p=0.31. Regarding 1298A>C polymorphism, in

Extended-Release Once-Daily Formulation of Tofacitinib: Evaluation of Pharmacokinetics Compared With Immediate-Release Tofacitinib and Impact of Food

The Journal of Clinical Pharmacology
2016, 56(11) 1362–1371
© 2016, The Authors. The Journal
of Clinical Pharmacology published by
Wiley Periodicals, Inc. on behalf of
American College of Clinical Pharma-
cology
DOI: 10.1002/jcph.734

Manisha Lamba, PhD¹, Rong Wang, MPh¹, Tracey Fletcher, BS², Christine Alvey, BS¹, Joseph Kushner IV, PhD¹, and Thomas C. Stock, DO²

Abstract

Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. An extended-release (XR) formulation has been designed to provide a once-daily (QD) dosing option to patients to achieve comparable pharmacokinetic (PK) parameters to the twice-daily immediate-release (IR) formulation. We conducted 2 randomized, open-label, phase I studies in healthy volunteers. Study A characterized single-dose and steady-state PK of tofacitinib XR 11 mg QD and intended to demonstrate equivalence of exposure under single-dose and steady-state conditions to tofacitinib IR 5 mg twice daily. Study B assessed the effect of a high-fat meal on the bioavailability of tofacitinib from the XR formulation. Safety and tolerability were monitored in both studies. In study A (N = 24), the XR and IR formulations achieved time to maximum plasma concentration at 4 hours and 0.5 hours postdose, respectively; terminal half-life was 5.9 hours and 3.2 hours, respectively. Area under plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) after single- and multiple-dose administration were equivalent between the XR and IR formulations. In study B (N = 24), no difference in AUC was observed for fed vs fasted conditions. C_{max} increased by 27% under the fed state. On repeat administration, negligible accumulation (<20%) of systemic exposures was observed for both formulations. Steady state was achieved within 48 hours of dosing with the XR formulation. Tofacitinib administration as an XR or IR formulation was generally well tolerated in these studies.

Keywords

tofacitinib, once daily, extended-release, pharmacokinetics, multiple dose, food

Tofacitinib is an oral Janus kinase (JAK) inhibitor for the treatment of rheumatoid arthritis (RA). In cellular settings, tofacitinib preferentially inhibits signaling via JAK3 and/or JAK1 with functional selectivity over signaling via pairs of JAK2.^{1,2} Inhibition of the JAK pathway blocks signaling through the common γ -chain-containing receptors for multiple proinflammatory cytokines.³

The pharmacokinetic (PK) profile of tofacitinib is characterized by rapid absorption and elimination, with time to maximum plasma concentration (t_{max}) 0.5 to 1 hour and terminal half-life ($t_{1/2}$) approximately 3 hours.^{4,5} Tofacitinib is approved as an immediate-release (IR) formulation and may be administered at a dose of 5 mg twice daily (BID) for a total daily dose of 10 mg.

For chronic conditions, such as RA, a once-daily (QD) dosing option has the potential to optimize compliance,⁶ and may enhance patient convenience and ease of use. To facilitate QD dosing, an extended-release (XR) tablet formulation of tofacitinib has been developed using extrudable core system (ECS) osmotic delivery technology.⁷ Compared with conventional

bilayer, push-pull osmotic tablets, the ECS tablet consists of a single-layer osmotically active core surrounded by a semipermeable membrane with a drug delivery port in the membrane. This technology has been shown to enhance the upper limit of drug loading in osmotic tablets.⁷ The ECS tablet formulation of tofacitinib has been designed to achieve equivalence in total systemic exposure, as measured by area under the plasma concentration-time curve (AUC), relative to the IR formulation administered BID. In addition, the

¹ Pfizer Inc, Groton, CT, USA

² Pfizer Inc, Collegeville, PA, USA

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Submitted for publication 26 January 2016; accepted 7 March 2016.

Corresponding Author:

Manisha Lamba, PhD, Clinical Pharmacology, Pfizer Inc, Eastern Point Road, MS8260-2512, Groton, CT 06340
Email: Manisha.lamba@pfizer.com

XR formulation was engineered to provide similarity in other PK parameters, including maximum (C_{\max}) and minimum plasma concentration (C_{\min}) compared with the IR formulation.

The ECS tablets of tofacitinib were developed at a dose strength of 11 mg to provide a QD equivalent to IR 5 mg BID.⁸ The 10% increase in total daily dose of the XR formulation was necessary to match the AUC with the IR formulation. Evaluations using a preliminary version of the 11-mg strength of the ECS tablet formulation demonstrated equivalence of AUC and C_{\max} between the XR and IR tofacitinib formulations.⁸

Here, we report the results of PK evaluations from 2 key phase 1 studies of the tofacitinib XR 11-mg formulation in healthy volunteers. The first study compared the PK between the IR and XR formulations of tofacitinib under both single- and multiple-dose conditions. The second study assessed the effect of a high-fat meal on the PK of the XR formulation of tofacitinib. In both studies, the proposed commercial image of the XR formulation was evaluated.

Methods

Subjects

Both study protocols were approved by the Institutional Review Boards and/or Independent Ethics Committees at each of the investigational centers. The final protocols and informed consent documentation for the relative bioavailability study were approved by Comité d'Ethique Hospitalo-Facultaire Erasme-ULB Cliniques Universitaires de Bruxelles, and the food effect study was approved by Aspire Institutional Review Board at the investigational center. Signed and dated informed consent was obtained from each subject enrolled in the study, prior to screening. The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with International Conference on Harmonisation Good Clinical Practice Guidelines. All local regulatory requirements were followed.

The 2 phase 1 studies were conducted in adult healthy volunteers to characterize the PK profile of the XR formulation of tofacitinib. Eligible subjects were healthy (defined by detailed medical history and a full physical examination), male or female of non-childbearing potential, aged 18 to 55 years, with body mass index between 17.5 and 30.5 kg/m² and total body weight >45 kg. They were required to have no evidence of active, latent, or inadequately treated tuberculosis infection. Key exclusion criteria included use of CYP3A inhibitors (eg, ketoconazole or itraconazole) or inducers (eg, rifampin) within 14 days (or 5 half-lives, whichever was longer) prior to dosing;

evidence or history of significant diseases; clinically significant infections within 3 months or any infection within 7 days of screening; history of disseminated herpes simplex or recurrent or disseminated herpes zoster infection; and personal or family history of hereditary immunodeficiency.

Study Design

Single- and Multiple-Dose Relative Bioavailability Study (Study A). Study A (Pfizer study A3921212) was a randomized, open-label, 2-way crossover study of tofacitinib XR 11 mg QD and tofacitinib IR 5 mg BID. Twenty-four healthy male subjects were enrolled at a Pfizer Clinical Research Unit in Brussels, Belgium.

In this 2-period study, each period comprised a single-dose phase followed by a multiple-dose phase of the same formulation. Subjects were randomized to receive tofacitinib XR or IR tablets in a crossover fashion. The XR treatment consisted of a single dose of tofacitinib XR 11-mg tablet on day 1, followed by QD dosing of the XR formulation tablets from days 3 through 7. The IR treatment consisted of 2 doses of tofacitinib IR 5-mg tablets approximately 12 hours apart on day 1, followed by BID dosing (12 hours apart) of the IR formulation tablets on days 3 through 7. Figure 1 shows the treatment administration schema of the study. The multiple-dose phase continued for 5 days across both (XR and IR) treatments; therefore study day 7 was day 5 of the multiple-dose phase, and “day 5” when used elsewhere is referring to study day 7 unless otherwise indicated. The 2 periods were separated by a ≥72-hour washout from the last morning dose of the multiple-dose phase. In addition, between the single- and multiple-dose phases of each period, there was a ≥48-hour washout from the morning dose of the single-dose phase.

The objectives of the study were to evaluate the PK of the XR formulation and to demonstrate equivalence of extent of exposure following single- and multiple-dose administration of tofacitinib XR 11 mg QD and IR 5 mg BID. Safety and tolerability were monitored throughout the study.

Food Effect Study (Study B). Study B (NCT02084875; Pfizer study A3921180) was a randomized, open-label, single-dose, 2-period, 2-way crossover study conducted at California Clinical Trials Medical Group (Glendale, California). Twenty-four subjects (23 males and 1 female of nonchildbearing potential) were randomized to receive the tofacitinib XR 11-mg tablet under fasted conditions or fed conditions.

For the fasted treatment, subjects received a single tofacitinib XR 11-mg tablet with 240 mL water following a ≥10-hour overnight fast. The fed treatment consisted of a standard (US Food and Drug Administration) high-fat breakfast 30 minutes prior

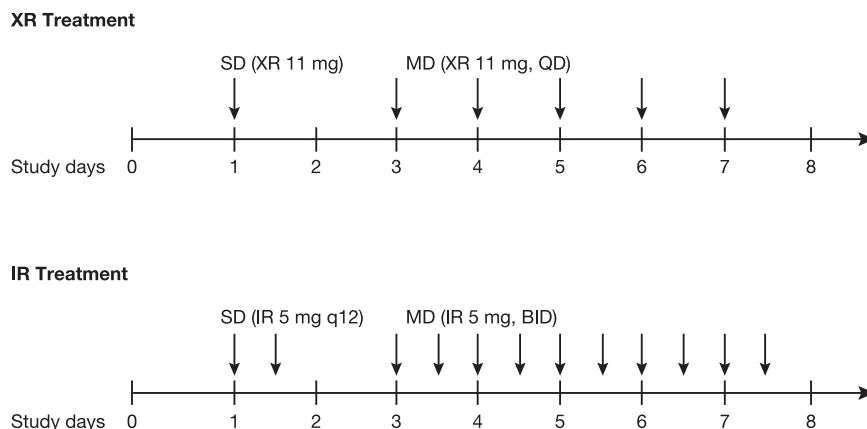


Figure 1. Schematic of study treatments and dosing (study A). Healthy volunteers received both XR and IR treatments in a randomized crossover fashion. Arrows represent treatment administration. BID, twice daily; IR, immediate-release; MD, multiple dose; q12, 12 hours apart; QD, once daily; SD, single dose; XR, extended-release.

to administration of a single tofacitinib XR 11-mg tablet with 240 mL water. The breakfast was a high-calorie (~800–1000 calories) and high-fat (~50% of total caloric content) test meal with approximately 150, 350, and 500–600 calories from protein, carbohydrate, and fat, respectively. Subjects were instructed to consume breakfast within 30 minutes or less. For each treatment, no additional food was allowed for ≥ 4 hours postdose, and water was withheld for 2 hours pre-dose and postdose. A ≥ 72 -hour washout separated the 2 periods.

The key study objectives were to evaluate the effect of food on the PK, safety, and tolerability of a single dose of the tofacitinib XR 11-mg tablet formulation.

PK Sampling and Analytical Method

During the single-dose phase (day 1) of study A, samples were collected predose (0 hours) and 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours postdose. For the IR treatment, blood samples were also collected at 0.5, 1, 2, 3, 4, 6, and 9 hours following the evening dose. During the multiple-dose phase of study A (day 5), blood samples were collected in a similar serial fashion predose and through 24 hours postdose. To establish steady state, predose blood samples were collected on the morning of days 3, 4, and 5 of the multiple-dose phase.

In study B, samples were collected predose (0 hours) and 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 36, and 48 hours postdose in each treatment period.

During each treatment period in study A and study B, 4-mL blood samples were collected to provide a minimum of 1.5 mL plasma for PK analysis. Samples were centrifuged for 10 minutes at 4°C at approximately 1700g and then stored at –20°C until analysis. Plasma samples were analyzed at WuXi AppTec (Shanghai, China) using a validated sensitive and specific high-performance liquid chromatography tandem mass spec-

trometry method. Calibration standard responses were linear over the range 0.100 to 350 ng/mL, and the lower limit of quantification for tofacitinib was 0.100 ng/mL.

Pharmacokinetic Calculations

In both studies, PK parameters were calculated for each subject and treatment using noncompartmental analysis of plasma concentration-time data with electronic noncompartmental analysis (eNCA; version 2.2.4), a Pfizer-developed and validated software system.

In study A, PK parameters for a single dose (day 1) included AUC from zero to infinity (AUC_{∞}), AUC for the daily dosing regimen of 24 hours (AUC_{24}), AUC for the dosing interval (AUC_{τ} , where $\tau = 12$ hours for IR treatment and 24 hours for XR treatment), $t_{1/2}$, C_{max} , and t_{max} . PK parameters for steady state (day 5) included AUC_{24} , AUC_{τ} , C_{max} , t_{max} , C_{min} , morning predose plasma concentration (C_{trough}), average plasma concentration (C_{av}), and degree of fluctuation at steady state calculated as $(C_{max} - C_{min})/C_{av}$.

For both XR and IR treatments, AUC_{τ} , C_{max} , and t_{max} for day 1 and AUC_{τ} , C_{max} , C_{min} , C_{av} , and degree of fluctuation for day 5 were calculated for the 0- to 24-hour daily dosing regimen. For the IR treatment, which was administered as 2 doses 12 hours apart, these parameters were also calculated for the morning (hours 0–12) and evening (hours 12–24) dosing intervals. AUC_{24} for the IR treatment, was calculated by adding AUC_{τ} from the morning and evening dosing intervals; AUC_{24} for the XR treatment is the same as AUC_{τ} . C_{av} was calculated as $AUC_{24}/24$ for the daily dosing interval and as $AUC_{\tau}/12$ for the morning and evening dosing intervals. For the IR treatment, $t_{1/2}$ was calculated from the terminal slope of the concentration-time profile on day 1 following administration of the evening dose.

In order to assess whether steady state had been achieved by day 5 of the multiple-dose phase, mean C_{trough} values on days 3, 4, and 5 of the multiple-dose

phase and 24 hours after the day 5 morning dose were plotted and visually examined. The accumulation ratio of AUC_{24} and C_{max} from single- to multiple-dose regimen was calculated for each treatment as the ratio of respective PK parameters from the multiple- to the single-dose phase.

For the food effect study (study B), standard PK parameters including t_{max} , $t_{1/2}$, C_{max} , and AUC_{∞} were calculated. In addition, effect of food on absorption delay was characterized by absorption lag time (t_{lag}).

Sample Size

A sample size of 22 evaluable subjects (11 subjects per sequence) in study A provided >90% power that the 90% confidence interval (CI) for the ratio of XR 11 mg to IR 10 mg administered as 2 5-mg doses (12 hours apart) for AUC_{∞} was within the equivalence interval of 80% to 125% under both single-dose and steady-state conditions. The calculations assumed the true mean ratio (XR/IR) for AUC of 0.95 and an estimate of within-subject standard deviation (SD) of 0.073 for natural log scale AUC following single- and multiple-dose administrations, obtained as an average from previous relevant Pfizer studies. This sample size also provided 80% coverage probability that the 90% CIs for the difference between XR and IR formulations were ± 0.098 for $\log_e C_{max}$ with an estimate of within-subject SD of 0.169.

In study B, the sample size of 24 PK-evaluable subjects provided 90% CIs for the difference between fed and fasted of ± 0.052 on the natural log scale for AUC_{∞} with 80% coverage probability assuming an estimate of within-subject SD of 0.094 for $\log_e AUC_{\infty}$ obtained for the selected formulation under its fed and fasted states.

Statistical Analysis

In both studies natural log-transformed PK parameters were analyzed using a mixed-effects model implemented using Proc Mixed in SAS V9.2. Sequence, period, and treatment were fixed effects, and subject within sequence was a random effect. Estimates of adjusted means differences (Test-Reference) and 90% CIs were obtained from the above models and exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios. For study A, the IR formulation was the Reference treatment, and the XR formulation was the Test treatment. For study B, tofacitinib XR 11-mg tablet administered under the fasted state was the Reference treatment, and the XR tablet administered under the fed state was the Test treatment.

To assess relative bioavailability under single-dose conditions (day 1) in study A, AUC_{∞} and C_{max} were analyzed; AUC_{24} , C_{max} , C_{min} , and C_{trough} were evaluated at steady state on day 5. Because the IR treatment

was administered twice a day (Figure 1), t_{max} , C_{max} , and C_{min} following administration of the morning dose were used as references for relative bioavailability assessments with the XR treatment, which was also administered in the morning.

The effect of food in study B was assessed by analyzing AUC_{∞} and C_{max} . If the 90% CI for the adjusted geometric mean ratio for the evaluated PK parameter fell wholly within the 80% to 125% equivalence interval, equivalence between Test and Reference treatment was concluded for that parameter.

Results

Subjects

Twenty-four subjects were enrolled in each of the studies. In study A, all subjects were male, and most were white (87.5%). Mean (SD) age was 35.7 (10.8) years, and weight was 79.4 (11.0) kg. In study B, most subjects were male (95.8%), with 33.3% white, 37.5% black, and 29.2% Asian. Mean (SD) age was 34.5 (9.9) years, and weight was 74.3 (10.0) kg.

One subject in study A discontinued during the first treatment period (receiving tofacitinib IR 5 mg BID) due to a superficial fungal skin infection that was not considered treatment-related by investigator determination. Therefore, although PK data from this subject were available and used in the analysis of the IR formulation, no data were available for the XR formulation for this subject because the subject did not receive the XR formulation in the second treatment period. As a result, evaluable PK data were available for all subjects ($N = 24$) for the IR formulation and 23 subjects for the XR formulation.

One subject in study B discontinued during the second treatment period due to conflict with his or her work schedule; however, PK sampling was completed to 24 hours postdose, so PK data from this subject were included in the analysis.

Assessment of Relative Bioavailability Under Single- and Multiple-Dose Conditions

Mean concentration-time profiles of the IR and XR formulations after single-dose administration (day 1) and multiple-dose administration (day 5) are presented in Figure 2. Table 1 summarizes the PK parameters of the 2 formulations under both single- and multiple-dose conditions.

Consistent with the extended-release properties of the XR formulation, C_{max} on day 1 was reached later for the XR formulation (median t_{max} 4 hours) than for the IR formulation (median t_{max} following morning dose 0.5 hours), and $t_{1/2}$ was longer for the XR (mean 5.9 hours) compared with the IR formulation (mean 3.2 hours). Although C_{max} was achieved later with the XR formulation, mean C_{max} (36.7 ng/mL) was

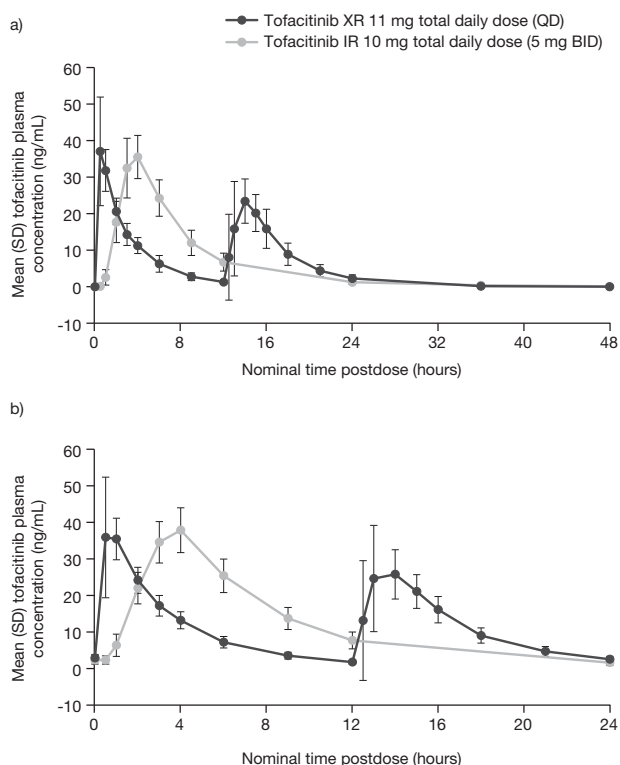


Figure 2. Mean (SE) tofacitinib plasma concentration-time profiles following XR 11 mg QD and IR 5 mg BID under (a) single-dose and (b) multiple-dose (for 5 days) conditions. BID, twice daily; IR, immediate-release; QD, once daily; SD, standard deviation; SE, standard error; XR, extended-release.

similar to that under the IR formulation (mean C_{max} following morning dose: 40.5 ng/mL).

As presented in Table 2, following single-dose administration, 90%CI for the adjusted geometric mean ratio for AUC_{∞} (XR/IR) was within the 80% to 125% equivalence interval, demonstrating equivalence of tofacitinib total daily exposure for tofacitinib XR 11 mg and tofacitinib IR 10 mg total daily dose. The 90%CI for the ratio of C_{max} values was also within the 80% to 125% equivalence interval.

Under steady-state conditions, the 90%CI for the adjusted geometric mean ratio for AUC_{24} and C_{max} (XR/IR) was within the 80% to 125% equivalence interval. Therefore, equivalence between tofacitinib XR 11 mg QD and tofacitinib IR 5 mg BID was demonstrated for tofacitinib total daily exposure and C_{max} . On day 5, the ratio of C_{min} values was 70.6% (90%CI: 59.0, 84.6), indicating approximately 29% lower C_{min} for the XR treatment than for the IR treatment. The ratio of adjusted geometric means for C_{trough} was 73.5% (90%CI: 57.7, 93.7), resulting in an approximately 26% lower C_{trough} for XR 11 mg QD compared with IR 5 mg BID.

Figure 3 shows the time course of mean C_{trough} values collected on the morning of day 3 through day 5

of the multiple-dose phase. Concentrations at 24 hours after the last dose on day 5 (ie, on day 6) were also included in this assessment. Predose concentrations were generally similar through day 6, indicating that steady state had been achieved within 48 hours of multiple-dose administration for both treatments. Multiple- to single-dose accumulation ratios were approximately 6% and 12% for C_{max} and AUC_{24} , respectively, for the XR formulation. This was consistent with the negligible accumulation observed for the IR formulation (4% and 12% for C_{max} and AUC_{24} , respectively). Degree of fluctuation of plasma concentration with the XR formulation (mean: 3.3) was approximately 13% lower than that for the IR formulation (mean: 3.8).

Effect of Food

Mean tofacitinib plasma concentration-time profiles following administration of tofacitinib XR 11-mg tablets under fasted and fed conditions are presented in Figure 4.

With food, tofacitinib absorption was slightly delayed, as observed by median t_{lag} of 0.5 hour (Table 3). Mean C_{max} for the fed treatment (48.3 ng/mL) was slightly higher than that for the fasted treatment (38.9 ng/mL) and was reached 1 hour later. Mean $t_{1/2}$ was shorter (4.4 hours) for fed treatment compared with fasted treatment (5.5 hours). Box plots comparing individual and geometric mean C_{max} and AUC_{∞} for fed and fasted treatments are presented in Figure 5. For both PK parameters, the range of individual exposures under the fed state was consistent and well within the range of individual exposures under the fasted state.

Statistical analysis (Table 3) showed that tofacitinib total exposure was equivalent under fed and fasted conditions: fed/fasted ratio for AUC_{∞} was 101.1% (90%CI: 96.9, 105.5) with the 90%CI wholly within the 80% to 125% equivalence interval. The ratio for the geometric mean of C_{max} was 127.2% (90%CI: 116.6, 138.8), suggesting a 27% increase in C_{max} with food.

Safety

There were no deaths, serious adverse events (AEs), severe AEs, or events of special interest in either study A or study B. One subject was permanently discontinued in study A due to an AE (superficial fungal skin infection) not considered to be related to tofacitinib treatment. In study A, 18 of the 24 subjects had at least 1 treatment-emergent AE (TEAE), with a total of 40 TEAEs reported. In study B, 2 of the 24 subjects had 1 TEAE. Most AEs in these studies were considered to be mild and related to study treatment. Among all AEs that were attributed to tofacitinib across both studies combined, the greatest number of subjects reported AEs in the system organ class of gastrointestinal disorders. The most frequently reported TEAEs were change

Table 1. Summary of PK Parameters of Tofacitinib Following Administration of XR 11 mg QD and IR 5 mg BID Formulations (Study A)

		Tofacitinib IR 5 mg BID (N = 24)		
PK Parameter (Units)	Tofacitinib XR 11 mg QD (N = 23)	Combined ^a (0–48 h)	Morning (0–12 h)	Evening (12–24 h)
Single-dose phase				
AUC _∞ (ng·h/mL)	259.8 (56.5)	247.9 (44.2)	—	—
AUC ₂₄ (ng·h/mL)	246.5 (50.6)	237.9 (40.8) ^b	—	—
AUC _τ (ng·h/mL)	246.5 (50.6)	—	117.7 (20.5)	120.3 (21.1)
C _{max} (ng/mL)	36.7 (6.8)	41.2 (9.7)	40.5 (10.3)	28.6 (6.4)
t _{max} (h)	4.0 (3.0, 4.0)	0.5 (0.5, 13.0)	0.5 (0.5, 1.0)	2.0 (0.5, 4.0)
t _{1/2} (h)	5.9 (1.8)	3.2 (0.8)	—	—
Multiple-dose phase (steady state)				
AUC ₂₄ (ng·h/mL)	272.9 (45.9)	266.1 (38.5)	—	—
AUC _τ (ng·h/mL)	272.9 (45.9)	—	133.3 (21.2)	132.8 (19.0)
C _{av} (ng/mL)	11.4 (1.9)	11.1 (1.6)	11.1 (1.8)	11.1 (1.6)
C _{min} (ng/mL)	1.3 (0.7)	1.5 (0.6)	1.6 (0.5)	1.5 (0.6)
C _{trough} (ng/mL)	2.2 (1.2)	2.70 (1.0)	—	—
C _{max} (ng/mL)	38.7 (6.1)	44.1 (11.6)	42.2 (11.1)	34.3 (8.9)
t _{max} (h)	4.0 (3.0, 4.0)	1.0 (0.5, 14.0)	0.5 (0.5, 1.0)	1.0 (0.5, 4.0)
Degree of fluctuation ^c	3.3 (0.5)	3.8 (0.9)	3.7 (0.9)	3.0 (0.6)

^aCombined morning and evening doses.

^bFor IR treatment, AUC₂₄ = AUC_τ for the morning (0–12 hours) + AUC_τ for the evening (12–24 hours) dosing intervals.

^cDegree of fluctuation calculated as (C_{max} – C_{min})/C_{av}.

All parameters are arithmetic mean (standard deviation) except median (range) for t_{max}.

AUC_∞, area under the plasma concentration-time curve from zero to infinity; AUC₂₄, area under the plasma concentration-time curve from 0 to 24 hours; AUC_τ, area under the plasma concentration-time curve during the dosing interval (24 hours for XR, 12 hours for IR); BID, twice daily; C_{av}, average plasma concentration over the dosing interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; C_{trough}, morning trough (predose) plasma concentration; IR, immediate-release; PK, pharmacokinetic; QD, once daily; t_{1/2}, terminal half-life; t_{max}, time to C_{max}; XR, extended-release.

Table 2. Statistical Comparison of PK Parameters of Tofacitinib Following XR 11-mg QD and IR 5-mg BID Treatments Under Single- and Multiple-Dose Conditions (Study A)

PK Parameter (Units)	Adjusted Geometric Means		Ratio	90%CI for Ratio ^a
	Tofacitinib XR 11 mg QD (Test)	Tofacitinib IR 5 mg BID (Reference)	(Test/Reference) of Adjusted Geometric Means ^a	
Single-dose phase				
AUC _∞ (ng·h/mL)	253.2	243.7	103.9	98.1, 109.3
C _{max} ^b (ng/mL)	36.0	39.2	91.8	83.3, 101.1
Multiple-dose phase (steady-state)				
AUC ₂₄ (ng·h/mL)	268.5	263.4	101.9	97.8, 106.3
C _{max} ^b (ng/mL)	38.2	40.9	93.4	84.1, 103.7
C _{trough} (ng/mL)	1.8	2.5	73.5	57.7, 93.7
C _{min} ^b (ng/mL)	1.0	1.5	70.6	59.0, 84.6

^aThe ratios (and 90%CI) are expressed as percentages.

^bRepresents values following morning dose of tofacitinib IR 5 mg.

AUC, area under the concentration-time curve; AUC_∞, AUC from 0 to infinity; AUC₂₄, AUC from 0 to 24 hours; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; C_{trough}, morning trough (predose) plasma concentration; IR, immediate-release; PK, pharmacokinetic; QD, once daily; XR, extended-release.

in bowel habit (n = 3) and diarrhea (n = 5). No major differences were observed between tofacitinib XR 11 mg QD and tofacitinib IR 5 mg BID in the frequency and/or type of AEs reported.

None of the reported AEs across the 2 studies were considered clinically important, and no clinically significant safety findings were noted on review of data collected from physical examinations,

clinical laboratory tests, vital signs, or electrocardiograms.

Discussion

Tofacitinib, an oral JAK inhibitor, is currently approved for the treatment of RA as an IR formulation, which is administered BID. This is the first published report of the full characterization of PK performance of an

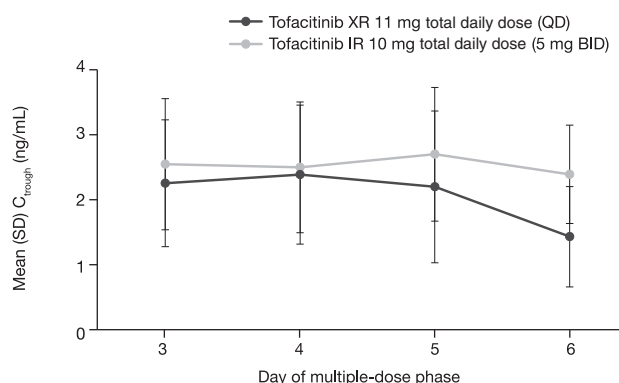


Figure 3. Mean (SE) C_{trough} by study day for tofacitinib XR 11 mg QD and tofacitinib IR 5 mg BID. Day 6 sample represents a 24-hour sample following last dose on day 5. BID, twice daily; C_{trough} , predose plasma concentration; IR, immediate-release; QD, once daily; SE, standard error; XR, extended-release.

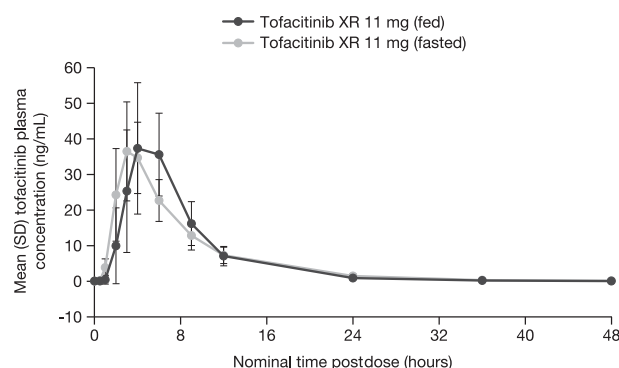


Figure 4. Mean (SE) tofacitinib plasma concentration-time profiles following single doses of tofacitinib XR 11-mg tablets under fasted and fed conditions. SE, standard error; XR, extended-release.

XR formulation of tofacitinib that may provide a once-daily dosing option.

These 2 phase 1 studies were designed to evaluate the PK and bioavailability of the XR formulation relative to the IR formulation and to assess the impact of food on drug absorption of the XR formulation. Safety and tolerability of the tofacitinib XR formulation in healthy volunteers were also assessed in these studies.

Regulatory guidance^{9,10} for modified or XR drug formulations recommends an assessment of relative bioavailability under single-dose and steady-state conditions. To achieve this objective, we consolidated the single- and multiple-dose assessments, separated by an appropriate washout, into a single study design (Figure 1). This design component, supported by the short PK half-life of tofacitinib, offered several advantages. For instance, relative bioavailability assessments between the 2 formulations under both single-dose and steady-state conditions were plausible within a single randomized crossover study, leading to an efficient study design. It also limited the number of healthy volunteers subjected to study drug. Finally, it enabled single-

Table 3. Descriptive Summary and Statistical Comparisons of PK Parameters of Tofacitinib Following Administration of a Single Dose of XR Formulation Under Fasted and Fed Conditions (Study B)

PK Parameter (Units)	Tofacitinib XR 11 mg Fed	Tofacitinib XR 11 mg Fasted
Summary statistics ^a		
t_{max} (h)	4.0 (3.0, 6.0)	3.0 (2.0, 6.0)
t_{lag} (h)	0.5 (0.0, 2.0)	0.0 (0.0, 0.5)
$t_{1/2}$ (h)	4.4 (1.5)	5.5 (1.3)
AUC_{∞} (ng·hr/mL)	274.6 (57.7)	273.2 (65.3)
C_{max} (ng/mL)	48.3 (11.3)	38.9 (12.9)
Statistical summary of effect of food on AUC_{∞} and C_{max} ^b		
AUC_{∞}	268.6	265.6
Fed/fastest ratio (90%CI) ^c	101.1 (96.9, 105.5)	
C_{max}	47.09	37.02
Fed/fastest ratio (90%CI) ^c	127.2 (116.6, 138.8)	

^aAll parameters are arithmetic mean (standard deviation) except: median (range) for T_{max} and T_{lag} .

^bAll parameters are geometric mean (geometric percentage coefficient of variation) except: median (range) for t_{max} and t_{lag} , arithmetic mean (standard deviation) for $t_{1/2}$.

^cThe ratios (and 90%CI) are expressed as percentages. Statistical comparisons are based on ratios of adjusted geometric means.

AUC_{∞} , area under the plasma concentration-time curve from 0 to infinity; CI, confidence interval; C_{max} , maximum plasma concentration; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; t_{lag} , lag time; t_{max} , time to C_{max} ; XR, extended-release.

multiple-dose PK comparisons for each formulation within the same study.

For single-dose relative bioavailability assessments between IR and XR formulations, it is common for the total daily IR dose to be administered as a single dose. By contrast, the IR 10-mg total daily dose in the current study (study A) was administered as 2 doses of IR 5 mg, 12 hours apart in the single-dose phase. This approach ensured that the total daily dose was equivalent over the least common time interval (ie, 24 hours) between the 2 formulations. This was designed in line with the current US Food and Drug Administration guidance for modified and XR drug products,⁹ and it also facilitated regimen-based comparisons between the XR and IR treatments under single-dose conditions.

Consistent with the properties of the XR formulation, C_{max} was reached later for the XR 11-mg than for IR 5-mg dose. Despite this, C_{max} was similar between the 2 formulations. The 2-fold longer $t_{1/2}$ of the XR formulation is likely to be a function of the absorption-limited disposition of tofacitinib due to extended drug release. Under both single-dose and steady-state conditions, the XR formulation demonstrated equivalence of AUC and C_{max} compared with the IR formulation as seen by 90%CI of the XR/IR ratio being completely contained within the 80% to 125% equivalence interval. Minimum plasma concentrations, as measured by C_{min} and C_{trough} , were approximately 29% and 26% lower, respectively, for the XR formulation (Table 2). Evaluation

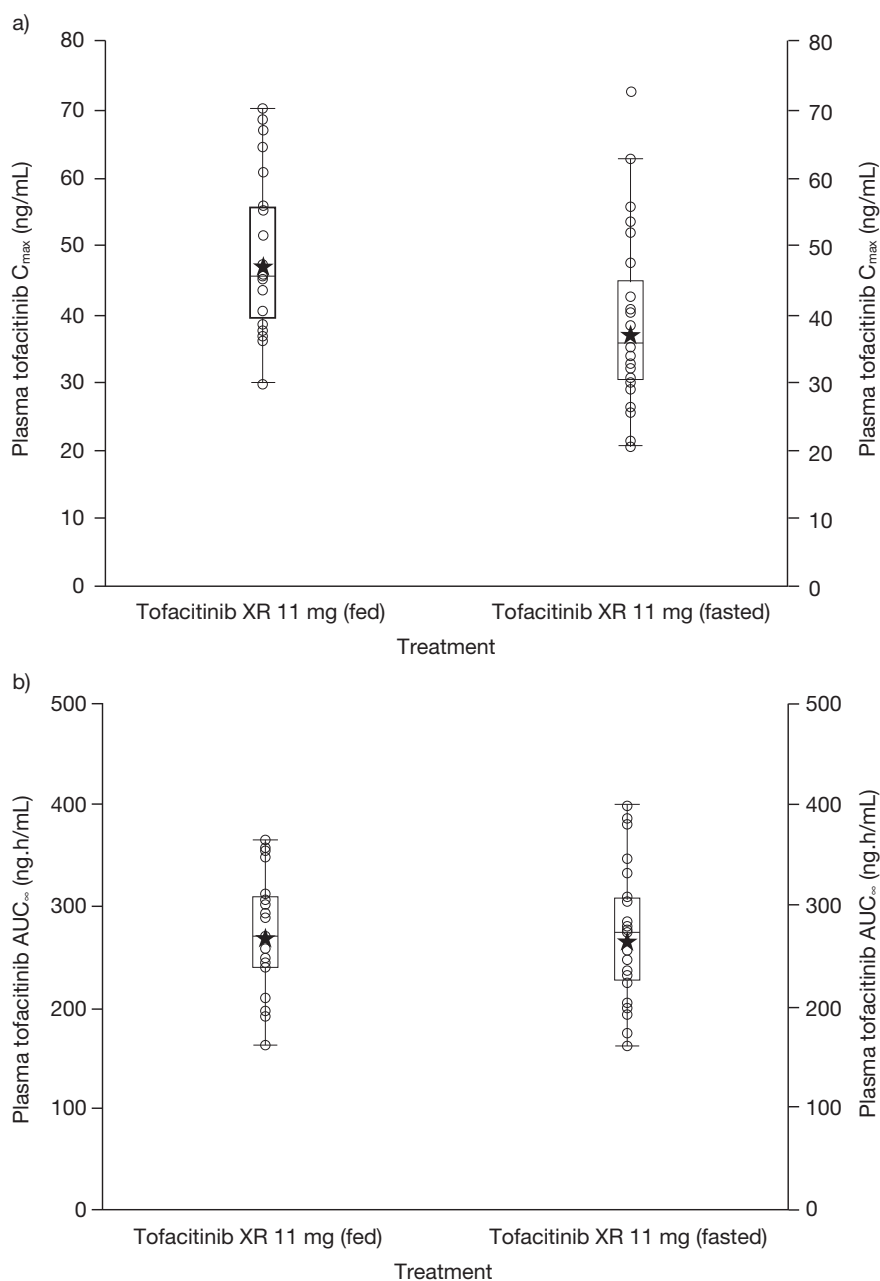


Figure 5. Individual and geometric mean (a) C_{max} and (b) AUC_{∞} of tofacitinib XR 11 mg under fasted and fed conditions. Stars represent geometric means, and circles represent individual volunteers. Box plot provides median and 25%/75% quartiles, with whiskers to the last point within $1.5 \times$ interquartile range. AUC_{∞} , area under the plasma concentration-time curve from zero to infinity; C_{max} , maximum plasma concentration; XR, extended-release.

of C_{trough} suggested that steady state was achieved within 48 hours of QD dosing of tofacitinib XR.

The accumulation of tofacitinib following repeat administration of the XR formulation was negligible (less than 20%), which is consistent with its $t_{1/2}$ of approximately 6 hours. These PK attributes are consistent with those of the IR formulation.

Interactions of food with XR drug formulations, which are designed to prolong or delay the rate of

drug release, are especially important. Results of the food effect evaluation with tofacitinib XR formulation showed a slightly prolonged T_{max} (fed vs fasted difference: 1 hour), a modest increase (27%) in C_{max} , and no change (geometric mean under fed conditions: 268.6 ng · h/mL, geometric mean under fasted conditions: 265.5 ng · h/mL) in AUC. This can potentially be explained by the properties of the ECS formulation and the physiology of the gastrointestinal system. A

high-fat meal may increase the gastric residence time, which would enable drug release to occur in the stomach for a prolonged period of time. As the meal is then emptied from the stomach and delivered to the small intestine, released drug is also presented to the small intestine, where it is readily absorbed. Therefore, in the fed state, a greater proportion of the drug is likely to be absorbed in the upper part of the small intestine, compared with the fasted state where deconvolution data from the XR formulation have suggested that the drug is absorbed throughout the intestinal tract as it transits through (data on file). This may lead to the observed increase in C_{\max} with food for the XR formulation. Total exposures, as measured by AUC_{∞} , were essentially similar under fed and fasted conditions and met the bioequivalence criteria. Given that the AUC was essentially the same under fasted or fed conditions, the modest increase in C_{\max} was not considered meaningful. In addition, a lack of significantly higher plasma concentrations in the initial time points of PK sampling, as shown in Figure 4, and slightly later T_{\max} under fed state confirms the absence of dose dumping. Furthermore, the range of exposures between the fed and fasted state was also similar.

The rate of drug release from the osmotic delivery system, a nondeformable dosage form, is generally independent of the effect of physiological factors such as the effect of food and pH.¹¹ Consequently, data from this study showing a lack of significant food effect on the ECS formulation of tofacitinib are consistent with other drugs formulated with osmotic delivery systems for which no impact of food on bioavailability is reported, including methylphenidate,¹² metoprolol,¹³ oxprenolol,¹⁴ and nifedipine.¹⁵ Although 11% to 30% increases in C_{\max} have been reported for the osmotic formulations of nifedipine and methylphenidate for fed vs fasted administration, no impact has been observed on extent of absorption.¹¹

Conclusions

The results of relative bioavailability assessments demonstrated total and peak exposures that were equivalent between XR and IR formulations of tofacitinib, as measured by AUC and C_{\max} . Consistent with a $t_{1/2}$ of approximately 6 hours, steady state with tofacitinib XR formulation was achieved within 48 hours of dosing. It showed negligible accumulation following repeat administration. Food had no effect on total systemic exposure of the XR formulation, but a modest increase in C_{\max} was observed. Tofacitinib XR 11-mg tablets were found to be generally well tolerated in healthy volunteers. The ECS tablet formulation of tofacitinib offers a convenient once-daily dosing option for tofacitinib.

Acknowledgments

The authors would like to thank the principal investigators of the clinical research units, Dr Constantine Kantaridis (Pfizer CRU) and Dr Esther Yoon (California Clinical Trials Medical Group). This study was sponsored by Pfizer Inc. Medical writing support, under the direction of the authors, was provided by Amanda Pedder of Complete Medical Communications and funded by Pfizer Inc.

Conflict of Interest Disclosure

M. Lamba, T. Stock, R. Wang, T. Fletcher, C. Alvey, and J. Kushner are employees and shareholders of Pfizer Inc.

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