Report on the Deliberation Results

March 15, 2013

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Xeljanz Tablets 5 mg
[Non-proprietary name]	Tofacitinib Citrate (JAN*)
[Applicant]	Pfizer Japan Inc.
[Date of application]	December 1, 2011

[Results of deliberation]
In the meeting held on March 13, 2013, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, the re-examination period is 8 years, and the drug substance and the drug product are both classified as powerful drugs.

[Conditions for approval]
The applicant is required to:
1. Conduct a drug use-results survey after the market launch, covering all patients treated with the drug, until data from a certain number of cases will be collected, in order to collect data on the safety and efficacy of the drug as soon as possible and to take necessary measures to ensure proper use of the drug.
2. Conduct an appropriate post-marketing surveillance study to fully assess the safety of the drug and to evaluate the safety and efficacy of long-term use of the drug, including the occurrence of infections etc.

**Japanese Accepted Name (modified INN)*

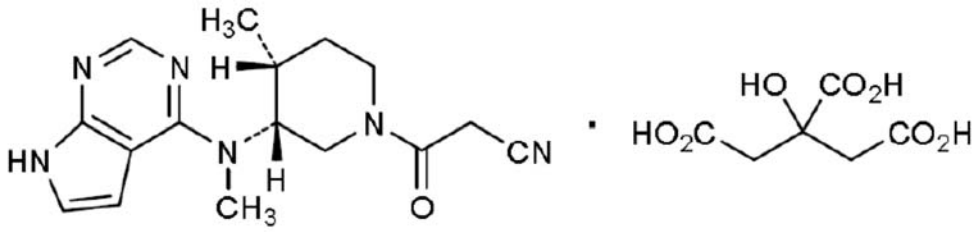
Review Report

February 28, 2013
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Xeljanz Tablets 5 mg
[Non-proprietary name]	Tofacitinib Citrate
[Name of applicant]	Pfizer Japan Inc.
[Date of application]	December 1, 2011
[Dosage form/Strength]	Each tablet contains Tofacitinib Citrate equivalent to 5 mg tofacitinib.
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{16}H_{20}N_6O \cdot C_6H_8O_7$

Molecular weight: 504.49

Chemical name:

3-{(3*R*,4*R*)-4-Methyl-3-[methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino]piperidin-1-yl}-3-oxopropanenitrile monocitrate

[Items warranting special mention]	None
[Reviewing office]	Office of New Drug IV

Review Results

February 28, 2013

[Brand name] Xeljanz Tablets 5 mg
[Non-proprietary name] Tofacitinib Citrate
[Name of applicant] Pfizer Japan Inc.
[Date of application] December 1, 2011

[Results of review]
Based on the submitted data, the efficacy of tofacitinib 5 mg twice daily in reducing signs and symptoms of rheumatoid arthritis such as joint pain in patients who have had an inadequate response to existing therapies has been demonstrated and it is considered to have clinical significance as a new therapeutic option. On the other hand, regarding safety, serious adverse drug reactions such as serious infections and malignancies may occur. Therefore, adequate safety measures for the clinical use of the product, like those for existing biologics, should be taken and a post-marketing surveillance study, covering all patients treated with the product, should be conducted, until data from a certain number of cases will be collected, in order to establish the safety profile of the product (including the detection of unknown adverse events) as soon as possible. Furthermore, a surveillance study to follow patients during long-term treatment for the occurrence of serious infections and malignancies, etc. should be conducted.

As a result of its review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions.

[Indication]
Rheumatoid arthritis in patients who have not adequately responded to conventional treatments

[Dosage and administration]
The usual dosage is 5 mg of tofacitinib given orally twice daily.

[Conditions for approval]
The applicant is required to:
1. Conduct a drug use-results survey after the market launch, covering all patients treated with the drug, until data from a certain number of cases will be collected, in order to collect data on the safety and efficacy of the drug as soon as possible and to take necessary measures to ensure proper use of the drug.
2. Conduct an appropriate post-marketing surveillance study to fully assess the safety of the drug and to evaluate the safety and efficacy of long-term use of the drug, including the occurrence of infections etc.

Review Report (1)

January 15, 2013

I. Product Submitted for Registration

[Brand name] [redacted] Tablets 5 mg, [redacted] Tablets 10 mg (proposed)
[Non-proprietary name] Tofacitinib Citrate
[Name of applicant] Pfizer Japan Inc.
[Date of application] December 1, 2011
[Dosage form/Strength] Each tablet contains Tofacitinib Citrate equivalent to 5 or 10 mg tofacitinib.
[Proposed indication]
Rheumatoid arthritis in patients who have not adequately responded to conventional treatments (including prevention of structural damage to joints and improvement in physical function)
[Proposed dosage and administration]
The usual dosage is 5 mg of tofacitinib given orally twice daily. The dose can be increased to 10 mg twice daily according to the patient's condition.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

The active ingredient of the product, Tofacitinib Citrate (tofacitinib), is an inhibitor of the Janus kinase (JAK) family discovered by Pfizer Inc. (US).

As drugs used for treatment of rheumatoid arthritis (RA), nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids etc. have been utilized for symptomatic relief. In recent years, disease-modifying anti-rheumatic drugs (DMARDs), primarily methotrexate (MTX), are introduced early in the course of the disease and furthermore, biologics such as anti-human tumor necrosis factor (TNF) agents are used in RA patients who have had an inadequate response to these conventional treatments. The JAK family of intracellular tyrosine kinases consists of JAK1, JAK2, JAK3, and tyrosine kinase (TyK) 2, which mediate signal transduction via interactions with type I and type II cytokine receptors. JAK1 and JAK3 (JAK1/3) are involved in signal transduction of cytokines, including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15, and IL-21, which are integral to lymphocyte activation, function, and proliferation and JAK1/2 or JAK1/TyK2 are involved in signal transduction of cytokines, including IL-6, interferon (IFN) γ, and IFNα, which play an important role in inflammation and immune responses, suggesting that JAK is associated with autoimmune diseases. Therefore, tofacitinib was developed as a therapeutic agent for RA.

In foreign countries, the clinical development of tofacitinib for the treatment of RA was initiated in 2002. In the US, 5 mg tofacitinib tablets[1] was approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to MTX[2] in November 2012. In Europe, the application to market tofacitinib was filed in [redacted] 2011 and is currently under review.

In Japan, the clinical development of tofacitinib was initiated in May 2007 and a marketing application for tofacitinib indicated for the treatment of RA has now been filed, utilizing foreign clinical data based on the ICH E5 guideline etc. The regulatory review of tofacitinib took longer than the standard review time due to a delay in the submission of the responses to PMDA's questions by the applicant.

Concerning the brand name for tofacitinib, as a similar name was identified during the course of a review in [redacted] and the proprietary name was changed, "[redacted] Tablets" proposed at the time of submission was changed to "Xeljanz Tablets."

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white powder and has been characterized by description, solubility, hygroscopicity, thermal analysis, dissociation constant (pKa), partition coefficient, and optical rotation. No other polymorphs have been observed.

The chemical structure of the drug substance has been confirmed by ultraviolet spectrophotometry (UV), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), mass spectrometry, and [redacted] structure determination.

2.A.(1).2) Manufacturing process

The drug substance is synthesized using [redacted], and as starting materials.

Based on the ICH guideline "Pharmaceutical Development (Revision 2)" (PFSB/ELD Notification No. 0628-1 dated June 28, 2010, "ICH Q8 Guideline") and the ICH guideline "Quality Risk Management" (PFSB/ELD Notification No. 0901004 dated September 1, 2006, "ICH Q9 Guideline"), Quality by Design (QbD) approaches were utilized and the following studies were mainly performed.

- Identification of critical quality attributes (CQAs) ([redacted] and [redacted] were defined as CQAs.)
- Identification of critical process parameters (CPPs) through quality risk assessment and design of experiments
- Modeling

[1] As in Japan, both the 5 mg and 10 mg twice-daily doses of tofacitinib were proposed, but the 5 mg twice-daily dose only was approved.
[2] As in Japan, the data on the efficacy of tofacitinib in preventing structural damage to joints and improving physical function were also included in the application. However, at the time of approval, as the study data did not show the prevention of structural damage to joints, the data regarding this effect were not included in the labeling.

[redacted], [redacted], and [redacted] steps have been defined as critical steps. [redacted] has not been established.

2.A.(1).3) Control of drug substance

The proposed specifications for the drug substance include content ([redacted]), description, identity (IR), purity (heavy metals, related substances [liquid chromatography (HPLC)], residual solvents [gas chromatography (GC)]), [redacted], residue on ignition, [redacted], and assay (HPLC).

2.A.(1).4) Stability of drug substance

Stability studies on the drug substance are as shown in Table 1. Based on the results of a photostability study, the drug substance is photostable.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	25°C	60%RH	[redacted] polyethylene bags ([redacted]) + [redacted] polyethylene drums ([redacted])	24 months
Accelerated	3 pilot-scale batches	40°C	75%RH		6 months

Based on the above, in accordance with the ICH guideline "Evaluation for Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003, "ICH Q1E Guideline"), a re-test period of 36 months has been proposed for the drug substance when stored in [redacted] polyethylene bags within [redacted] polyethylene drums at room temperature. The long-term stability study will continue up to 36 months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug substance is formulated as an immediate-release tablet. Each tablet contains 5 mg or 10 mg tofacitinib and the following excipients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, and film-coating agents (5 mg tablets, Opadry II White; 10 mg tablets, [redacted]).

The 5 mg tablet is white and the 10 mg tablet is [redacted] so that the two tablet strengths are distinguishable by color.

The oral powder for constitution and the intravenous formulation were used in phase I studies, the 1 mg and 5 mg uncoated tablets in phase II studies, and the 5 mg film-coated tablet in phase III studies. The to-be-marketed formulations are the 5 mg and 10 mg film-coated tablets.

2.A.(2).2) Manufacturing process

The manufacturing process for the drug product consists of [redacted], tableting, and film-coating. [redacted] step was defined as a critical step during the course of the review.

Based on the ICH Q8 and Q9 guidelines, QbD approaches were utilized and the following studies were mainly performed.

- Identification of CQAs ([redacted] and [redacted] observed in stability studies were defined as CQAs.)

- Identification of CPPs through quality risk assessment and design of experiments
- Development of design space (DS)
- Studies of [redacted] and [redacted] using models

2.A.(2).3) Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identity (HPLC, UV), purity (degradation products [HPLC]), [redacted], uniformity of dosage units (content uniformity testing [HPLC]), [redacted], and assay (HPLC).

2.A.(2).4) Stability of drug product

Stability studies on the drug product are as shown in Table 2. Based on the results of a photostability study, the drug product is photostable.

Table 2. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	25°C	60%RH	PTP	24 months
	3 pilot-scale batches	30°C	75%RH		24 months
Accelerated	3 pilot-scale batches	40°C	75%RH		6 months

Based on the above, in accordance with the ICH Q1E guideline, a shelf-life of 36 months has been proposed for the drug product when packaged in PTP ([redacted]/aluminum foil/polyvinyl chloride laminated film/aluminum foil) and stored at room temperature. The long-term stability study will continue up to 36 months.

2.B Outline of the review by PMDA

Based on the submitted data and the following reviews, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

2.B.(1) Control strategy for CQAs of drug substance

The applicant explained CQAs of the drug substance and parameters that have an effect on CQAs as follows: [redacted] that is considered to affect [redacted] and [redacted] different impurities that are present in [redacted] were defined as CQAs of the drug substance. In order to identify quality attributes and process parameters that had potential to impact safety and/or efficacy, risk assessment was performed. As a result, while the parameters of Step[redacted] ([redacted] reaction) and Step[redacted] ([redacted]) had no effect on CQAs, Step[redacted] ([redacted], [redacted] and [redacted]) was considered to affect [redacted] and the removal rate of impurities. Thus, Step[redacted] is considered a critical step that affects drug substance CQAs.

[redacted] was studied based on computational modeling, development-scale, multivariate experiments, and pilot-/commercial-scale manufacturing experience. As a result, it was confirmed that it does not affect [redacted] within the established acceptance criteria, and under all conditions tested in [redacted] step, the intended [redacted] was obtained. In [redacted] step, it was decided to perform [redacted] by [redacted] in order to prevent [redacted] due to [redacted] and rigorous quality control on its [redacted] content as a CPP.

Impurities were defined as CQAs of the drug substance. As the design of experiments for [redacted] reaction in Step[redacted], multivariate experiments focusing on [redacted] content, [redacted] content, [redacted] concentration ([redacted]kg), [redacted], and [redacted] were performed. As a result, under the conditions of [redacted] concentration of [redacted] and [redacted] contents of [redacted] and [redacted], unreacted [redacted] remained (when [redacted] in the reaction system was [redacted]%, [redacted]% remained) while under the conditions of [redacted] contents of, [redacted] and [redacted], the amounts of [redacted] and [redacted] (impurities) [redacted] were [redacted] ([redacted], [redacted]% and [redacted]%, respectively). PMDA asked the applicant to explain the ability of [redacted] and [redacted] steps [redacted] this step to remove impurities, with a view to confirming the appropriateness of control values and the robustness of the manufacturing process.

The applicant explained as follows:
The results of a study using commercial-scale batches showed that the removal rate of [redacted] in [redacted] and [redacted] steps was [redacted]%. Based on the results of [redacted] in the design of experiments for [redacted] reaction, the removal rates of [redacted] and [redacted] were [redacted]% and [redacted]%, respectively. [redacted] or [redacted] was not detected in any scale-up batch. Furthermore, the robustness of these steps to remove impurities can be assured by adequate quality control on [redacted] amount of [redacted], [redacted], and [redacted] [redacted] content, which were identified as parameters that affect the removal of impurities in [redacted] and [redacted] steps.

PMDA accepted the above response and concluded that [redacted] and [redacted] different impurities, which were defined as CQAs of the drug substance, are adequately controlled.

2.B.(2) Drug substance manufacturing process
The applicant explained that [redacted] and [redacted] etc., which were shown not to impact the quality of the drug substance within the ranges studied, were not "matters subject to approval," but were internally controlled. PMDA considered that in the case of the manufacturing process developed using a QbD strategy, which of [redacted] and [redacted] etc. are controlled as matters subject to approval, may be determined according to the control strategy based on quality risk management, but at least the attributes required to grasp the manufacturing process need to be controlled as "matters subject to approval." Accordingly, PMDA requested the applicant to control [redacted] such as [redacted] and [redacted] in a critical reaction step, e.g. the formation of the basic structure of the drug substance, as "matters subject to approval."

The applicant agreed and took appropriate action.

2.B.(3) [redacted] process for drug product

The applicant explained the impact of [redacted], [redacted], or [redacted] step before [redacted] step on [redacted] as follows:

In order to evaluate the role of [redacted] and [redacted] operations, [redacted] under the condition of [redacted] of [redacted] step, [redacted] of [redacted] step, or [redacted] of [redacted] mm, [redacted] was compared with [redacted] in the standard [redacted] process. As a result, when [redacted] step was [redacted], the relative standard deviation of [redacted] was [redacted], indicating that [redacted] step is important to meet [redacted]. However, as there was no correlation between [redacted] in [redacted] step and [redacted], [redacted] step was not defined as a critical step. On the other hand, although [redacted] had little impact on [redacted] within the ranges studied, as [redacted] is a typical [redacted] of [redacted] step, [redacted] was defined as a key process parameter (KPP) in order to recognize the importance of [redacted] step and make it clearer that the potential of [redacted] step to affect [redacted] should be considered when making changes to the manufacturing process in future. The potential effect of [redacted] on [redacted] was investigated, which showed that [redacted] does not affect [redacted].

PMDA pointed out as follows:

It is not appropriate to define [redacted] as a KPP in order to recognize the importance of [redacted] step, etc. and this should be reconsidered. Even if [redacted] step has no CPP, [redacted] process operation itself, which [redacted] through [redacted], is important for [redacted] and this process step is essential to assure [redacted] of [redacted] process and should be defined as [redacted] step.

The applicant responded that [redacted] will be recategorized as a non-critical process parameter (non-CPP) and [redacted] step will be defined as a critical step.

2.B.(4) Process parameters included in DS

PMDA requested the applicant to specify the interactions of parameters investigated and the parameters included in DS if DS was developed and the control range was determined based on DS for the process parameters described in the manufacturing process, which is a matter subject to approval.

The applicant agreed and took appropriate action.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

As primary pharmacodynamic studies, tofacitinib inhibition of the JAK family, cell proliferation, signal transducer and activator of transcription (STAT) phosphorylation, and IFNγ production was determined and the effects of tofacitinib in collagen-induced arthritis (CIA) and adjuvant-induced arthritis (AIA) animal models, the effect of tofacitinib in a delayed-type hypersensitivity model, and the effects of tofacitinib on circulating lymphocyte subsets were investigated. Secondary pharmacodynamic studies evaluated the effects of tofacitinib on lipids in peritoneal macrophages and cholesterol synthesis and transport in the AIA model and the effects of tofacitinib on circulating reticulocytes, receptors, ion channels, enzymes, and transporters. Safety pharmacology studies evaluated the potential effects of tofacitinib on the central nervous,

cardiovascular, respiratory, renal/urinary, and gastrointestinal systems and convulsions. Safety pharmacology studies were non-GLP studies performed before the implementation of the ICH S7A guideline, except for some studies that evaluated the potential effects of tofacitinib on the cardiovascular system (4.2.1.3.2 to 4.2.1.3.3, 4.2.1.3.5). No pharmacodynamic drug interaction studies were performed. For oral administration studies, doses are expressed as free base equivalents.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) Inhibition of JAK family (4.2.1.1.1 to 4.2.1.1.3)

The inhibitory effects of tofacitinib on the activity of recombinant human JAK1, 2, 3, and TyK2 (phosphorylation activity) were determined in a mobility shift assay. The 50% inhibitory concentrations (IC_{50}) of tofacitinib for JAK1, 2, 3, and TyK2 were 3.2, 4.1, 1.6, and 34 nmol/L, respectively. Tofacitinib is an ATP-competitive inhibitor of JAK1, 2, 3, and TyK2 and the inhibition constants (Ki) were 0.68, 0.97, 0.24, and 4.4 nM, respectively. The IC_{50} values of tofacitinib on approximately 80 kinases other than the JAK family were all ≥1 μmol/L, mostly ≥10 μmol/L.

3.(i).A.(1).2) Inhibition of cell proliferation (4.2.1.1.4 to 4.2.1.1.9)

The inhibitory effects of tofacitinib on JAK1 and JAK3 dependent, human IL-2-stimulated, T-cell proliferation, and human, cynomolgus monkey, and murine mixed lymphocyte proliferation were determined and the IC_{50} values were 11, 87, 52, and 115 nmol/L, respectively. The IC_{50} of tofacitinib for inhibition of human GM-CSF-stimulated, JAK2-dependent, erythroleukemia cell line (HU03) proliferation was 324 nmol/L. Tofacitinib did not inhibit bovine fetal serum-stimulated, JAK-independent, human foreskin fibroblast proliferation at concentrations up to 10,000 nmol/L.

3.(i).A.(1).3) Inhibition of STAT phosphorylation (4.2.1.1.11 to 4.2.1.1.12)

The inhibitory effects of tofacitinib on STAT phosphorylation stimulated by a broader panel of cytokines in human whole blood were determined by flow cytometry. The IC_{50} values of tofacitinib for inhibition of IL-2-, IL-4-, IL-7-, IL-15-, or IL-21-stimulated, JAK1/3-dependent, STAT phosphorylation were 25 to 111 nmol/L. The IC_{50} values of tofacitinib for inhibition of IL-10- or IFNα-stimulated, JAK1/TyK2-dependent, STAT phosphorylation were 44 to 206 nmol/L. The IC_{50} values of tofacitinib for inhibition of IL-6- or IFNγ-stimulated, JAK1/2-dependent, STAT phosphorylation were 54 to 406 nmol/L. The IC_{50} of tofacitinib for inhibition of GM-CSF-stimulated, JAK2-dependent, STAT phosphorylation was 1377 nmol/L. Tofacitinib exhibited a more potent inhibitory effect on JAK1/3-dependent, STAT phosphorylation than on JAK2-, JAK1/2-, and JAK1/TyK2-dependent, STAT phosphorylation.

3.(i).A.(1).4) Inhibition of IFNγ production (4.2.1.1.10)

The inhibitory effects of tofacitinib on cytokine-stimulated IFNγ production in human peripheral blood mononuclear cells (PBMC) and human whole blood were evaluated. The IC_{50} values for inhibition of IL-2-stimulated, JAK1/3-dependent, IFNγ production were 26 nmol/L in PBMC and 34 nmol/L in whole blood and the IC_{50} values for inhibition of IL-12-stimulated, JAK2/TyK2-dependent, IFNγ production were 129 nmol/L in PBMC and 501 nmol/L in whole blood.

The applicant explained that the above *in vitro* studies (4.2.1.1.1 to 4.2.1.1.12) showed that tofacitinib potently inhibits JAK1/3-dependent signaling and moderately inhibits JAK1/TyK2- and JAK2/2-dependent signaling.

3.(i).A.(1).5) Effects in animal models of arthritis

3.(i).A.(1).5).(a) Assessment of the effect of tofacitinib on inflammatory cytokines and chemokines in CIA model (4.2.1.1.15)

Arthritis in male mice (n = 6 or 7/timepoint/group) was induced by injection of two doses (the initial and challenge doses) of 50-μg chicken type-II collagen. The challenge dose was given 3 weeks after the initial dose. The effects of tofacitinib on plasma levels of inflammatory cytokines and chemokines in this CIA model were assessed. The mice were given a single oral dose of 10 or 50 mg/kg of tofacitinib 43 days after the initial sensitization and plasma levels of inflammatory cytokines and chemokines were determined at 4, 12, 24, and 48 hours post-dose. The 10 mg/kg group showed reductions in plasma levels of IL-6, keratinocyte-derived chemokine (KC), and monocyte chemotactic protein (MCP)-5 at 4 hours post-dose and reductions in plasma levels of interferon inducible protein-10 (IP-10) and MCP-5 at 12 hours post-dose, compared with the vehicle group. The 50 mg/kg group showed reductions in plasma levels of IL-6, KC, MCP-5, IP-10, and monokine induced by interferon gamma (MIG) at 4 hours post-dose and reductions in plasma levels of MCP-5, IP-10, and MIG at 12 hours post-dose, compared with the vehicle group.

3.(i).A.(1).5).(b) Prophylactic efficacy of tofacitinib in CIA model (4.2.1.1.14)

The efficacy of tofacitinib administration initiated prior to arthritis development was studied in the CIA model in male mice (n = 6-12/group). The mice were orally given tofacitinib 1 to 100 mg/kg once daily (QD), 1 to 100 mg/kg twice daily (BID), or 0.5 to 50 mg/kg twice daily for 35 days starting from 22 days after the initial sensitization (1 day after the challenge). There were dose-dependent decreases in arthritis severity scores[3] and the incidence of arthritic symptoms and the 50% effective doses (ED_{50}) were 15 and 29 mg/kg for BID and QD, respectively. The inhibitory effects of tofacitinib on STAT phosphorylation stimulated by cytokines in mouse whole blood 1 hour after the last dose were determined. The ED_{50} values of tofacitinib for inhibiting IL-15-stimulated, JAK1/3-dependent, STAT5 phosphorylation were 3 and 3 mg/kg for BID and QD, respectively, the ED_{50} values of tofacitinib for inhibiting IL-6-stimulated, JAK1/2-dependent, STAT1 phosphorylation were 5 and 7 mg/kg, respectively, and the ED_{50} values of tofacitinib for inhibiting GM-CSF-stimulated, JAK2-dependent, STAT5 phosphorylation were >100 and 91 mg/kg, respectively.

3.(i).A.(1).5).(c) Therapeutic efficacy of tofacitinib in CIA model (4.2.1.1.16 to 4.2.1.1.18)

The efficacy of tofacitinib administration initiated following arthritis development was studied in the CIA model in male mice (n = 8/timepoint/group). The mice were orally given 50 mg/kg of tofacitinib twice daily for 8 days starting from 48 days after the initial sensitization. Tofacitinib decreased the arthritis severity scores on Treatment Day 4 compared with the vehicle group. After the last dose, there were reductions in inflammatory cell infiltrates into tissues and joint cavity and F4/80+ and CD3+ cells and a trend towards reduced bone resorption in the tofacitinib group compared with the vehicle group. At ≥4 hours after the first dose, tofacitinib caused reductions in plasma levels of granulocyte colony stimulating factor (G-CSF), IL-6,

[3] Mice were evaluated for inflammation by scoring the severity of each paw (score 0 = no swelling or redness; score 1 = swelling or redness of the digits of the paw or both, score 2 = gross swelling of the whole paw or deformity or both, score 3 = ankylosis of the joints) with a maximum score of 12.

IP-10, and MCP-1 and serum amyloid A level and tissue (rear paw) levels of G-CSF, IL-6, and MCP-1, compared with the vehicle group. In the arthritic rear paw tissues, tofacitinib inhibited the expression of STAT1 responsive genes by 4 hours after the first dose, the expression of natural killer (NK) cell-related genes by 24 hours after the first dose, and the expression of macrophage-, B cell-, T-cell-, and osteoclast-related genes by the last day of dosing, compared with the vehicle group.

3.(i).A.(1).5).(d) Pharmacokinetic/pharmacodynamic modeling in CIA model (4.2.1.1.19)

A pharmacokinetic/pharmacodynamic modeling study was conducted using data from prophylactic tofacitinib studies of oral administration (QD and BID) and subcutaneous infusion using an osmotic pump in the CIA model (4.2.1.1.14). When tofacitinib was administered by subcutaneous infusion, the $ECave_{50}$ was 44 nmol/L, the IC_{50} for IL-15-stimulated, JAK1/3-dependent, STAT5 phosphorylation was 42 nmol/L, and the IC_{50} for GM-CSF-stimulated, JAK2-dependent, STAT5 phosphorylation was 4379 nmol/L, indicating that inhibition of JAK1/3 signaling, but not JAK2 signaling, plays the key role in the efficacy of tofacitinib. When tofacitinib was orally administered twice daily, the C_{ave} at the ED_{50} (6.0 mg/kg) was 90 nmol/L and the duration of blood concentrations above the IC_{50} for JAK1/3-dependent, STAT5 phosphorylation (42 nmol/L) was 12 hours per day and when tofacitinib was orally administered once daily, the C_{ave} at the ED_{50} (33.5 mg/kg) was 128 nmol/L and the duration of blood concentrations above the IC_{50} for JAK1/3-dependent, STAT5 phosphorylation was 8.5 hours per day, indicating that continuous inhibition of JAK1/3 signaling is not necessarily required for the optimal efficacy of tofacitinib and effectiveness can be achieved if blood concentrations remain above the IC_{50} for a certain duration each day.

3.(i).A.(1).5).(e) Prophylactic and therapeutic efficacy of tofacitinib in AIA model (4.2.1.1.20 to 4.2.1.1.21)

Arthritis in female rats (n = 8 or 12/group) was induced by tail injections of heat-killed *Mycobacterium butyricum* (three injection sites, 50 µL/site, 15 mg/mL). The efficacy of tofacitinib administration initiated prior to arthritis development was studied in this AIA model. The rats were orally given tofacitinib 0.06 to 60 mg/kg twice daily or 0.06 to 18.51 mg/kg once daily for 11 days starting from 11 days after immunization. Tofacitinib treatment resulted in dose-dependent decreases in the rear paw volume on Treatment Day 10 and the ED_{50} values for BID and QD were <0.06 mg/kg and 0.66 mg/kg, respectively. Tofacitinib treatment also resulted in dose-dependent decreases in peripheral blood neutrophil counts (PBNC) and the ED_{50} values for BID and QD were 1.7 mg/kg and 16.7 mg/kg, respectively. Tofacitinib reduced the plasma levels of IL-6, IL-17, and the acute-phase protein α2-macroglobulin in a dose-dependent manner and increased plasma cholesterol levels in a dose-dependent manner.

The efficacy of tofacitinib administration initiated following arthritis development was studied in the AIA model in female rats (n = 6-12/group). The rats were orally given tofacitinib 0.02 to 18.5 mg/kg twice daily or 0.06 to 18.5 mg/kg once daily or once every other day (QOD) for 7 days starting from 14 days after immunization. Tofacitinib treatment resulted in dose-dependent decreases in the rear paw volume on Treatment Day 7 and the ED_{50} values were 0.15 mg/kg, 6.3 mg/kg, and 7.1 mg/kg for BID, QD, and QOD, respectively. Tofacitinib reduced PBNC in a dose-dependent manner and increased plasma cholesterol levels in a dose-dependent manner.

3.(i).A.(1).5).(f) Therapeutic efficacy of tofacitinib in AIA model (4.2.1.1.22 to 4.2.1.1.24)

The efficacy of tofacitinib administration initiated following arthritis development was studied in the AIA model in female rats (n = 13-29/group). The rats were orally given 6.2 mg/kg of tofacitinib once daily for 7 days starting from 16 days after immunization with adjuvant.[4] On Treatment Day 4, tofacitinib treatment resulted in decreases in the paw volume compared with the vehicle group. Tofacitinib treatment caused decreases in the plasma levels of IL-6 and IL-17 at 4 hours after the first dose and decreases in the plasma levels of IL-6, IL-17, and α2-macroglobulin on the following day of the last dose. In the rear paw tissues, a decrease in IL-6 level at 4 hours after the first dose and decreases in the levels of IL-6, MCP-1, receptor activator of nuclear factor kappa-B ligand (RANKL), growth-related oncogene (Gro)/KC, and MIP-1α and increases in the levels of leptin and vascular endothelial growth factor (VEGF) after the last dose were observed.

AIA rats were treated with tofacitinib with the same schedule as in the above study and histopathological and immunohistochemical analyses were performed. As a result, there were reductions in inflammatory cell infiltrates into tissues and joint cavity, osteoclast-mediated bone resorption, ED-1 (CD68)+ cells, and CD3+ cells.

Furthermore, AIA rats were treated with tofacitinib with the same schedule and transcription profiling was performed. In the arthritic rear paw tissues, tofacitinib treatment resulted in decreases in the expression levels of STAT1 responsive genes and NK cell-related genes at 4 hours after the first dose and decreases in the expression levels of macrophage-, B cell-, T-cell-, and osteoclast-related genes on Treatment Day 7.

3.(i).A.(1).6) Effect of tofacitinib in delayed type hypersensitivity model (4.2.1.1.25)

Male mice (n = 9-20/group) were infused intravenously with sheep red blood cells and rechallenged subcutaneously in the footpad 5 days later. The effects of tofacitinib on delayed type hypersensitivity reactions were studied in this acute inflammation model. When 0.5, 1.5, 5, or 15 mg/kg/day of tofacitinib was continuously administered subcutaneously using an osmotic mini pump from 2 days prior to the initial sensitization, footpad swelling at 24 hours after the rechallenge was inhibited in a dose-dependent manner by tofacitinib. Footpad swelling was inhibited by 86.2% in the tofacitinib 15 mg/kg/day group compared with the vehicle group and the ED_{50} was 2 mg/kg/day.

3.(i).A.(1).7) Effects on circulating lymphocyte subsets (4.2.1.1.26)

Male and female cynomolgus monkeys (n = 5/group) were orally administered 10, 50, or 200 mg/kg of tofacitinib in three divided doses, 7 hours apart and the effects of tofacitinib on circulating lymphocyte counts were investigated using flow cytometry. There were no effects on circulating T cells, B cells, or NK cells up to 2 weeks after the last dose.

3.(i).A.(2) Secondary pharmacodynamics

[4] Heat-killed *Mycobacterium butyricum*

Since dose-dependent increases in plasma cholesterol observed in AIA rats (4.2.1.1.20 to 4.2.1.1.21) were also noted in RA patients treated with tofacitinib in clinical studies [see "4.(iii) Summary of clinical efficacy and safety"], the effects of tofacitinib on lipid regulation were evaluated.

3.(i).A.(2).1) Evaluation of tofacitinib effects on lipids in peritoneal macrophages in AIA model (4.2.1.2.1-1 to 4.2.1.2.1-2)

AIA female rats (n = 4-8/group) were orally administered 3 or 10 mg/kg of tofacitinib twice daily for 8 days starting from 16 days after immunization with adjuvant.[5] On and after Treatment Day 4, cholesteryl ester (CE) and basal lipid levels and the uptake of lipids after lipid loading in peritoneal macrophages were increased in the vehicle group (AIA model group) compared with untreated animals, which were all decreased in a dose-dependent manner by tofacitinib.

3.(i).A.(2).2) Evaluation of tofacitinib effects on cholesterol synthesis and transport in AIA model (4.2.1.2.2)

AIA female rats (n = 12/group) were given a continuous intravenous infusion of ^{13}C-cholesterol 14 days after immunization with adjuvant[5] to evaluate the effects of tofacitinib on cholesterol transport. The rats were orally administered 2 or 10 mg/kg of tofacitinib twice daily for 12 days starting from 7 days after immunization. Plasma total cholesterol (TC) and CE levels and the rate of cholesterol esterification were decreased and the level of haptoglobin, which inhibits cholesterol esterification, was increased in the vehicle group (AIA model group) compared with untreated animals while plasma TC and CE levels, the rate of cholesterol esterification, apolipoprotein A-I (ApoA I), and paraoxonase activity (a marker of HDL function) were increased in a dose-dependent manner by tofacitinib.

3.(i).A.(2).3) Effects of tofacitinib on circulating reticulocytes (4.2.1.2.3)

Since EPO signaling is mediated by two molecules of JAK2, the effects of tofacitinib on EPO-stimulated increases in blood reticulocytes in male and female cynomolgus monkeys (n = 3/sex/group) were examined. The monkeys received 5 mg/kg of oral tofacitinib twice daily for 16 days with a single subcutaneous dose of 100 U/kg of EPO on Day 2. The percent increases in reticulocyte count from baseline (before administration of EPO) in the tofacitinib and vehicle groups were 125% and 236%, respectively, 3 days after EPO administration and 192% and 254%, respectively, 5 days after EPO administration, and EPO-induced increases in reticulocytes were inhibited by tofacitinib. In the tofacitinib group, reticulocyte count increased by 510% from baseline by 1 week after the last dose, which returned to baseline levels over time. While there were no effects of EPO on hemoglobin concentration or red blood cell count in the vehicle group, hemoglobin concentration and red blood cell count were decreased and these decreases were sustained up to 2 weeks after the last dose in the tofacitinib group. The C_{max} (unbound) in the 5 mg/kg group was 248 ng/mL, which was approximately 3.3-fold the C_{max} (unbound, 75 ng/mL[6]) observed in RA patients following administration of tofacitinib 10 mg twice daily.

3.(i).A.(2).4) Effects on receptors, ion channels, enzymes, and transporters (4.2.1.2.4 to 4.2.1.2.5)

[5] Heat-killed *Mycobacterium butyricum*

[6] Calculated by multiplying the C_{max} (122.96 ng/mL) in a Japanese phase II study (A3921039) by the unbound fraction (fu) 0.61.

The effects of 10 μmol/L tofacitinib on a broad panel of receptors, ion channels, enzymes, and transporters were investigated *in vitro*. Inhibition was observed for the MT3 (ML2) receptor, vascular endothelial growth factor receptor (VEGFR) 1, calmodulin-dependent protein kinase (CaMK) 2α, and LynA kinase and the IC_{50} values were 5.3, 3.7, 12, and 2.3 μmol/L, respectively (1624, 1156, 3749, and 719 ng/mL, respectively), which were 22-, 15-, 50-, and 10-fold the C_{max} in RA patients (10 mg BID).

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effects on central nervous system (Reference data 4.2.1.3.1)

Male mice (n = 3/group) received a single oral dose of 3.2, 10, 32, 100, 320, or 1000 mg/kg of tofacitinib and the effects of tofacitinib on general symptoms and behavioral observations (modified Irwin's test) and spontaneous locomotor activity were assessed. No effect was observed at ≤32 mg/kg. Decreased spontaneous locomotor activity, hunched to flattened posture, splayed hind limbs, increased eye closure, and vocalization were observed at 100 mg/kg. At 320 mg/kg, in addition to the findings noted at 100 mg/kg (excluding increased eye closure), death, twitches upon movement, mild seizures, decreases in body tone, toe pinch, tail pinch, and corneal responses, and exploratory behavior, ptosis, a decrease in positional passivity, a decrease in respiration, tremors, and loss of righting reflex were observed. At 1000 mg/kg, death occurred and the intensity of the symptoms noted at 320 mg/kg increased. The C_{max} (unbound) in the 100 mg/kg group was 3216 ng/mL, which was approximately 43-fold the C_{max} in RA patients (10 mg BID).

3.(i).A.(3).2) Pro- or anti-convulsive activity (Reference data 4.2.1.3.1)

Male mice (n = 20/group) received a single oral dose of 3.2, 10, or 32 mg/kg of tofacitinib. Tofacitinib had no effects on intraperitoneal pentylenetetrazol (85 mg/kg)-induced muscle twitching, myoclonus, and tonic extension.

3.(i).A.(3).3) Effects on cardiovascular system

3.(i).A.(3).3).(a) *In vivo* studies (4.2.1.3.5, Reference data 4.2.1.3.1, Reference data 4.2.1.3.4)

Male cynomolgus monkeys (n = 4/group) received a single oral dose of 100 or 300 mg/kg of tofacitinib and the effects of tofacitinib on the cardiovascular system were assessed. There was no effect on heart rate at 100 mg/kg. At 300 mg/kg, heart rate increased at 2 to 3 hours after dosing and heart rate was approximately 43% higher compared with the vehicle group at 3 hours after dosing. There were no effects on blood pressure or ECG at either dose level. The C_{max} (unbound) in the 300 mg/kg group was 2152 ng/mL, which was approximately 29-fold the C_{max} in RA patients (10 mg BID).

Male rats (n = 4/group) received a single oral dose of 10 or 100 mg/kg of tofacitinib. There were no effects on mean arterial pressure or heart rate at 10 mg/kg while mean arterial pressure decreased by 37 mmHg and heart rate increased by about 100 bpm in the 100 mg/kg group. The C_{max} (unbound) in the 100 mg/kg group was 7336 ng/mL, which was approximately 98-fold the C_{max} in RA patients (10 mg BID).

Female rats (n = 8/group) were orally administered tofacitinib for 5 days at 10, 30, or 75 mg/kg/day. At ≥10 mg/kg, dose-dependent decreases in systolic blood pressure, diastolic blood pressure, and mean blood pressure (−5 to −17 mmHg) were observed by 2 hours post-dose on Days 1, 3, and 5, transient increases in heart rate

(+30 to +67 bpm) were observed by 2 hours post-dose on Day 1 and/or Day 5, and body temperature decreases occurred during the dosing period (up to −0.37°C). At 30 and 75 mg/kg, in addition to the above findings, decreases in heart rate (−27 to −39 bpm) were observed at 8 to 12 hours post-dose on Days 1 and 5. The C_{max} (unbound) in the 10 mg/kg group was 2176 ng/mL, which was approximately 29-fold the C_{max} in RA patients (10 mg BID).

3.(i).A.(3).3).(b) Effect on hERG channel current (4.2.1.3.2, Reference data 4.2.1.3.1)

Using HEK293 cells expressing hERG potassium channels, the effect of tofacitinib on hERG channel current was evaluated using the whole-cell patch-clamp technique. Tofacitinib at 10, 30, and 100 μmol/L (3124, 9372, and 31,240 ng/mL, respectively) inhibited hERG current amplitude by 0.8%, 3.6%, and 17.8%, respectively, and the IC_{50} was ≥100 μmol/L. 100 μmol/L (31,240 ng/mL) was approximately 417-fold the C_{max} in RA patients (10 mg BID).

In a separate study, tofacitinib inhibited hERG current amplitude by 6.4% at 10 μmol/L (3124 ng/mL).

3.(i).A.(3).3).(c) Effect on action potential in isolated canine cardiac Purkinje fibers (4.2.1.3.3)

The effect of tofacitinib on cardiac action potential in isolated canine cardiac Purkinje fibers was evaluated. Tofacitinib at 0.1, 1, and 10 μmol/L (31.2, 312, and 3124 ng/mL, respectively) had no effects on the action potential durations at 50% and 90% repolarization (APD_{50} and APD_{90}), resting membrane potential (RMP), action potential amplitude (APA), or maximal depolarization velocity (V_{max}).

3.(i).A.(3).3).(d) Effect on isolated rat aorta (Reference data 4.2.1.3.1)

The effect of tofacitinib on the contraction induced by KCl (30 mmol/L) or norepinephrine (1 μmol/L) in isolated rat aorta was evaluated. Tofacitinib at 0.1, 1, 10, and 100 μmol/L (31.2, 312, 3124, and 31,240 ng/mL, respectively) caused dose-dependent relaxation and inhibited KCl-induced contraction by 1%, 18%, 83%, and 100%, respectively, and norepinephrine-induced contraction by 1%, 16%, 69%, and 100%, respectively.

The applicant explained as follows:

As changes related to this effect, decreases in blood pressures were observed after a single dose of 100 mg/kg of tofacitinib or 5-day administration of ≥10 mg/kg of tofacitinib in *in vivo* studies in rats, whereas no decreases in blood pressure were noted after a single dose of 300 mg/kg of tofacitinib in an *in vivo* study in monkeys. Adverse events of "blood pressure decreased," "hypotension," and "orthostatic hypotension" reported in clinical studies were analyzed. As a result, among 4816 subjects treated with tofacitinib in Japanese and foreign phase II, phase III, and long-term extension studies in RA patients, 2 subjects had "blood pressure decreased," 8 subjects had "hypotension," and 3 subjects had "orthostatic hypotension" and the incidences of these events were low. Thus, there are no safety concerns associated with the inhibition of vasoconstriction by tofacitinib in humans.

3.(i).A.(3).3).(e) Effect on isolated guinea pig right atria (Reference data 4.2.1.3.1)

Tofacitinib at 0.1, 1, 10, or 100 μmol/L (31.2, 312, 3124, or 31,240 ng/mL, respectively) had no effect on the spontaneous beating rate of isolated guinea pig right atria.

3.(i).A.(3).4) Effects on respiratory system (Reference data 4.2.1.3.1)

Male rats (n = 4/group) received a single oral dose of 10 or 100 mg/kg of tofacitinib. While there were no effects on arterial pH, PO_2, or PCO_2 up to 120 minutes post-dose in the 10 mg/kg group, arterial PO_2 increased by about 10 mmHg in the 100 mg/kg group. The C_{max} (unbound) in the 100 mg/kg group was 7336 ng/mL, which was approximately 98-fold the C_{max} in RA patients (10 mg BID).

3.(i).A.(3).5) Effects on renal/urinary system (Reference data 4.2.1.3.1)

Male rats (n = 12/group) received a single oral dose of 3, 10, or 100 mg/kg of tofacitinib and the effects of tofacitinib on the renal/urinary system were assessed. There were no effects on urinary volume or electrolyte excretion at ≤10 mg/kg while potassium excretion elevated by 104% and chloride excretion and urinary volume decreased by 77% and 32%, respectively, in the 100 mg/kg group compared with the vehicle control group (0.5% methylcellulose). The C_{max} (unbound) in the 100 mg/kg group was 7336 ng/mL, which was approximately 98-fold the C_{max} in RA patients (10 mg BID).

3.(i).A.(3).6) Effects on gastrointestinal system (Reference data 4.2.1.3.1)

Male rats (n = 5 or 6/group) received a single oral dose of 10, 30, or 100 mg/kg of tofacitinib and tofacitinib was evaluated, using ^{51}Cr (10,000 cpm) orally administered 60 minutes later as a marker, for its effects on gastric emptying and gastrointestinal transit. While there were no effects in the 10 mg/kg group, tofacitinib at ≥30 mg/kg decreased gastric emptying to 68% and reduced intestinal motility to 79%. The C_{max} (unbound) in the 30 mg/kg group was 3511 ng/mL, which was approximately 47-fold the C_{max} in RA patients (10 mg BID).

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Mechanism of action of tofacitinib in RA

The applicant explained the mechanism of action of tofacitinib in RA as follows:

The sustained secretion of cytokines is involved in the pathogenesis of progressive chronic RA (Brennan FM, et al. *J Clin Invest.* 2008;118:3537-3545). The JAK family is known to mediate the signaling of a variety of cytokines (Walker JG, et al. *J Rheum*. 2005;32:1650-1653). For example, JAK1/3 is involved in IL-2-, IL-4-, IL-7-, IL-9-, IL-15-, and IL-21-induced lymphoid development, homeostasis, activation, and proliferation (Russell SM, et al. *Science*. 1995;270:797-800, Thomis DC, et al. *Curr Opin Immunol.* 1997;9:541-547), JAK1/2 or JAK1/TyK2 is involved in IL-6-, IFNγ-, IFNα-, and IL-10-induced inflammation and immune responses (Murray PJ, et al. *J Immunol*. 2007;178:2623-2629), and two molecules of JAK2 are involved in the signaling of hematopoietic cytokines and hormones, such as EPO, IL-3, GM-CSF, prolactin, leptin, and growth hormone. Tofacitinib is an inhibitor of the JAK family and can block multiple cytokine pathways simultaneously. In pharmacology studies, tofacitinib was shown to potently inhibit JAK1/3-dependent signaling *in vitro*, decrease inflammatory cytokines such as IL-6 and MCP-1 *in vivo*, and reduce tissue and plasma levels of inflammatory cytokines, inflammation of joints, and osteoclast-mediated bone resorption in arthritis models. Based on these pharmacology data and a report that JAK3 expression was increased in

synovial tissue taken from RA patients (Walker JG, et al. *Ann Rhem Dis*. 2006;65:149-156) etc., tofacitinib is expected to work against RA by inhibiting the expression of inflammatory cytokines.

PMDA concluded as follows:
Based on the submitted data, the pharmacological effects of tofacitinib have been demonstrated and tofacitinib can be expected to be effective in RA.

3.(i).B.(2) Effects of tofacitinib on lipid regulation

There were dose-dependent increases in plasma cholesterol in the AIA model. PMDA asked the applicant to explain the possibility that this event induces cardiovascular events.

The applicant explained as follows:
Since it has been reported that in RA patients, reductions in HDL-cholesterol, LDL-cholesterol, and total cholesterol have been noted (Choy E, et al. *Ann Rheum Dis.* 2009;68:460-469) and dose-dependent elevations in LDL-cholesterol and HDL-cholesterol were observed within 1 to 3 months of tofacitinib treatment in clinical studies [see "4.(iii) Summary of clinical efficacy and safety"], a secondary pharmacodynamic study evaluated the effects of tofacitinib on lipid regulation. In this study, development of AIA in rats impaired the reverse cholesterol transport process resulting in a decrease in the rate of cholesterol esterification and a decrease in total plasma cholesterol, but tofacitinib was shown to increase cholesterol clearance by increasing cholesterol esterification and fecal excretion etc. and restore the reverse cholesterol transport. It is considered that this effect of tofacitinib is mediated via increased lecithin cholesterol acyltransferase (LCAT) activity and plasma ApoA I, etc. (LCAT is involved in the esterification of free cholesterol; and ApoA I is a cofactor for LCAT). Since reverse cholesterol transport is a pathway by which accumulated cholesterol is transported from the vessel wall to the liver for excretion (Ohashi R, et al. *Q J Med.* 2005;98:845-856) and the atherogenic indice of the ratio of LDL to HDL and the ratio of apolipoprotein B100 to ApoA etc. were unchanged by tofacitinib in clinical studies, elevations in plasma cholesterol associated with tofacitinib are not suggestive of a pre-atherogenic state and are unlikely to be related to the occurrence of cardiovascular events.

PMDA considers as follows:
As human relevance of the mechanism by which tofacitinib increased the reverse cholesterol transport in the AIA model animals is unknown, the relationship between elevations in plasma cholesterol associated with tofacitinib and the possible occurrence of cardiovascular events needs to be assessed carefully based on clinical study data.

3.(i).B.(3) Effects of tofacitinib on immune and hematopoietic systems

The applicant discussed the mechanism of tofacitinib effects on the immune and hematopoietic systems observed in non-clinical studies as follows:
Decreases in circulating lymphocytes, NK cells, and T cells and lymphoid depletion in lymphoid tissues observed in rat and monkey toxicity studies are considered due to the inhibition of JAK3 by tofacitinib because as described above, JAK3 is known to mediate the signaling of cytokines that play key roles in lymphoid development and homeostasis etc. (Di Santo JP. *Annu Rev Immunol.* 2006;24:257-286, Ma A, et al. *Annu Rev*

Immunol. 2006;24:657-679, Rochman Y, et al. *Nat Rev Immunol.* 2009;9:480-490), and moreover, decreases in circulating NK cells and T cells and defective lymphoid development etc. have been reported in JAK3 knockout mice and humans with JAK3 mutations (Nosaka T, et al. *Science.* 1995;270:800-802, Roberts JL, et al. *Blood.* 2004;103:2009-2018, Ghoreschi K, et al. *Immunological Reviews.* 2009;228:273-287).

Taking also into account that B-cell lymphopenia has been reported also in IL-7- or JAK3-deficient mice (Nosaka T, et al. *Science.* 1995;270:800-802, Peschon JJ, et al. *J Exp Med.* 1994;180:1955-1960, von Freeden-Jeffry U, et al. *J Exp Med.* 1995;181:1519-1526), JAK1/3-mediated IL-7 signaling is critical for B cell development in rodents and decreases in circulating B cells observed in a rat toxicity study are considered due to the inhibition of this signaling pathway by tofacitinib. On the other hand, since it has been reported that B-cell numbers are normal in IL-7- and JAK3-deficient severe combined immune deficiency (SCID) patients (Roberts JL, et al. *Blood.* 2004;103:2009-2018, Ghoreschi K, et al. *Immunological Reviews.* 2009;228:273-287, Puel A, et al. *Nat Genet.* 1998;20:394-397), IL-7 does not play a key role in B cell development in monkeys or humans and tofacitinib is unlikely to cause decreases in B cells.

In rat and monkey toxicity studies, decreases in red blood cell parameters, reticulocytes (%), platelet count, eosinophil count, and basophil count were observed. Also in a secondary pharmacodynamic study, EPO-stimulated increases in reticulocytes were inhibited by tofacitinib. These findings are considered due to the inhibition of hematopoietic growth factor signaling and the signaling of cytokines related to eosinophil and basophil development (IL-5 and IL-3, respectively) via inhibition of JAK2 by tofacitinib (Witthuhn B, et al. *Cell.* 1993;74:227-236, Foster PS, et al. *J Exp Med.* 1996;183:195-201, Ohmori K, et al. *J Immunol.* 2009;182:2835-2841). Concerning immunosuppression via JAK1/3 inhibition and an inhibitory effect on erythropoiesis via inhibition of JAK2 as described above, the toxic and therapeutic concentrations of tofacitinib overlap.

PMDA considers as follows:
As tofacitinib effects on the immune and hematopoietic systems are as anticipated from its pharmacological properties, it is necessary to determine the clinical dose carefully, based on clinical study data, after careful consideration of the therapeutic benefit against the risk of adverse drug reactions related to these pharmacological effects.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

As absorption, distribution, metabolism, excretion, and drug-drug interaction data, the results from oral and intravenous administration studies in mice, rats, rabbits, dogs, and monkeys were submitted. Tofacitinib and radiolabeled tofacitinib (^{14}C-tofacitinib) were used in pharmacokinetic studies and unchanged drug in plasma and serum was quantitated by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Lower limit of quantitation, 0.5 or 1 ng/mL in plasma, 10 ng/mL for ^{14}C-tofacitinib in plasma, 1 or 5 ng/mL in serum). Radioactivity in plasma, urine, and bile was quantitated by liquid scintillation counter (LSC) and tissue concentrations of radioactivity were quantitated using whole-body autoradiography (Lower limit of quantitation, 0.034 μg eq./g).

Unless otherwise specified, doses are expressed as free base equivalents and pharmacokinetic parameters are expressed as the mean or the mean ± standard deviation (SD).

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose studies (4.2.2.2.1 to 4.2.2.2.4, 4.2.2.4.3 to 4.2.2.4.4)

Pharmacokinetic parameters of unchanged drug and radioactivity in plasma or serum in male and female rats, female rabbits, male and female dogs, and male and female monkeys following a single oral or intravenous administration of tofacitinib or ^{14}C-tofacitinib were as shown in Table 3. Tofacitinib was rapidly absorbed after oral administration and the oral bioavailability of tofacitinib was 43.3% in male rats, 129% in female rats, 43% in dogs, and 48% in monkeys.

Table 3. Pharmacokinetic parameters in rats, rabbits, dogs, and monkeys following a single dose of tofacitinib or ^{14}C-tofacitinib

Species	Dose (mg/kg)	N	Route of administration	Unchanged drug						Radioactivity			
				C_{max} (ng /mL)	T_{max} (h)	AUC_{0-t} (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	Vss (L/kg)	C_{max} (ng eq./mL)	T_{max} (h)	AUC_{0-t} (ng eq.·h/mL)	$t_{1/2}$ (h)
Rat	10 [a]	3 males	p.o.	796 ± 133	0.5	1130 ± 270	ND	-	-	2410 ± 186	0.5	4330 ± 243	ND
		3 females		2390 ± 187	0.5	4610 ± 199	ND	-	-	3590 ± 106	0.5	7590 ± 316	ND
	10 [b]	4 males		2400 ± 948	0.31	2750 ± 838	2.0	-	-	-	-	-	-
		4 females		3670 ± 1430	0.25	6910 ± 1720	1.5	-	-	-	-	-	-
	5 [b]	4 males	i.v.	ND	-	3180 ± 1160	2.8	29.0 ± 10.7	1.55 ± 0.34	-	-	-	-
		4 females		ND	-	2730 ± 2200	1.8	42.3 ± 19.5	1.43 ± 0.16	-	-	-	-
Rabbit	30 [a]	4 females	p.o.	-	-	-	-	-	-	16,800 ± 1750	0.875	69,800 ± 8240	2.40
Dog	5 [a]	2 males, 2 females	p.o.	1020 ± 255	0.5	2330 ± 423 [c]	ND	-	-	-	-	-	-
	3 [a]	6 males, 2 females	i.v.	ND	-	3250 ± 1610 [c]	1.2	19.4 ± 9.8	1.8 ± 0.8	-	-	-	-
Monkey	5 [a]	2 males, 1 female	p.o.	791 ± 157	1.1	2280 ± 338 [c]	ND	-	-	-	-	-	-
	5 [a]	2 males	p.o.	513	1.5	1240	1.4	-	-	2820	1.5	10,400	8.9
		2 females	p.o.	783	1.0	1820	1.2	-	-	2730	1.5	8650	6.3
	3 [a]	4 males	i.v.	ND	-	2850 ± 543 [c]	2.1	18.2 ± 4.2	1.7 ± 0.2	-	-	-	-

Mean or Mean ± SD
ND = Not determined, - = No data, C_{max} = Maximum observed concentration, T_{max} = Time to reach C_{max}, AUC = Area under the concentration-time curve, $t_{1/2}$ = Apparent terminal elimination half-life, CL = Systemic clearance, Vss = Apparent volume of distribution at steady state
p.o. = Oral administration, i.v. = Intravenous administration
a: Plasma concentration, b: Serum concentration, c: $AUC_{0-\infty}$ (ng·h/mL)

3.(ii).A.(1).2) Repeat-dose studies (Toxicokinetics) (4.2.3.2.3 to 4.2.3.2.6, 4.2.3.4.1.1, 4.2.3.4.2.3, 4.2.3.5.2.3 to 4.2.3.5.2.5, 4.2.3.5.4.2, 4.2.3.7.7.3)

Toxicokinetics were evaluated in the following repeat-dose studies of tofacitinib: mouse 6-month and rat 6-week, 6-month, and 2-year oral administration studies, a 12-day oral administration study in pregnant rats, an oral administration study in juvenile rats (35 days for females, 50 days for males), a 13-day oral administration study in pregnant rabbits, and monkey 1-month and 39-week oral administration studies, etc.

Mice (n = 3/sex/timepoint) were administered tofacitinib orally for 6 months at doses of 25, 75, or 200 mg/kg/day. At the end of dosing (Week 20), the C_{max} values of unchanged drug in serum in females and males were 1900 and 1380 ng/mL, respectively, in the 25 mg/kg/day group, 4120 and 3530 ng/mL, respectively, in the 75 mg/kg/day group, and 3270 and 8260 ng/mL, respectively, in the 200 mg/kg/day group and the AUC_{0-24} values were 1860 and 1990 ng·h/mL, respectively, in the 25 mg/kg/day group, 8880 and 6210 ng·h/mL, respectively, in the 75 mg/kg/day group, and 13,700 and 20,800 ng·h/mL, respectively, in the 200 mg/kg/day group. C_{max} and AUC_{0-24} increased with increasing dose and although the AUC_{0-24} was higher in females than males at 75 mg/kg/day and in males than females at 200 mg/kg/day, no apparent gender differences were observed.

Rats (n = 3/sex/timepoint) were administered tofacitinib orally for 6 months at doses of 1, 10, or 100 mg/kg/day. On Day 1, the C_{max} values of unchanged drug in serum in females and males were 179 and 75.0 ng/mL, respectively, in the 1 mg/kg/day group, 2460 and 761 ng/mL, respectively, in the 10 mg/kg/day group, and 10,900 and 9000 ng/mL, respectively, in the 100 mg/kg/day group and the AUC_{0-24} values were 513 ng·h/mL and NR[7], respectively, in the 1 mg/kg/day group, 5850 and 2030 ng·h/mL, respectively, in the 10 mg/kg/day group, and NR[8] and 52,300 ng·h/mL, respectively, in the 100 mg/kg/day group. At Week 26, the C_{max} values in females and males were 382 and 120 ng/mL, respectively, in the 1 mg/kg/day group, 3040 and 1640 ng/mL, respectively, in the 10 mg/kg/day group, and 10,600 and 9670 ng/mL, respectively, in the 100 mg/kg/day group and the AUC_{0-24} values were 742 ng·h/mL and NR[7], respectively, in the 1 mg/kg/day group, 7680 and 3440 ng·h/mL, respectively, in the 10 mg/kg/day group, and 68,800 and 43,200 ng·h/mL, respectively, in the 100 mg/kg/day group. C_{max} and AUC_{0-24} increased with increasing dose and systemic exposure was greater in females than males at ≤10 mg/kg/day, but no apparent gender differences were observed at 100 mg/kg/day. There was a trend towards slight increases in the C_{max} and AUC_{0-24} after repeated dosing at ≤10 mg/kg/day.

Pregnant rats (n = 5/group) were orally administered tofacitinib from gestation day 6 through gestation day 17 at doses of 1, 10, or 30 mg/kg/day in the initial study and at doses of 30, 100, or 300 mg/kg/day in a repeat of the initial study. At the end of dosing (Day 12), the C_{max} values of unchanged drug in serum in the 1, 10, and 30 mg/kg/day groups of the initial study and the 30, 100, and 300 mg/kg/day groups[9] of the repeat study were 185 ± 18.7, 2690 ± 465, 4900 ± 449, 6360 ± 1510, 9390 ± 1130, and 14,400 ng/mL, respectively, and the AUC_{0-24} values were 516 ± 117, 8400 ± 1420, 24,000 ± 2590, 29,400 ± 3060, 73,800 ± 16,600, and 108,000 ng·h/mL, respectively, and C_{max} and AUC_{0-24} increased with increasing dose.

Doses of tofacitinib were administered orally at 1, 10, or 100 mg/kg/day to juvenile rats (n = 3 or 4/sex/timepoint) from postnatal day 21 to 55 (35 days) for females and from postnatal day 21 to 70 (50 days) for males. On Day 1, the C_{max} values of unchanged drug in serum in females and males were 109 and 90.5 ng/mL, respectively, in the 1 mg/kg/day group, 1610 and 1320 ng/mL, respectively, in the 10 mg/kg/day group, and 11,000 and 8640 ng/mL, respectively, in the 100 mg/kg/day group and the AUC_{0-24} values were 336 and 281 ng·h/mL, respectively, in the 1 mg/kg/day group, 6720 and 4890 ng·h/mL, respectively, in the 10 mg/kg/day group, and 71,200 and 69,100 ng·h/mL, respectively, in the 100 mg/kg/day group. At the end of dosing (females, Day 35; males, Day 50), the C_{max} values in females and males were 249 and 95.3 ng/mL, respectively, in the 1 mg/kg/day group, 2890 and 1440 ng/mL, respectively, in the 10 mg/kg/day group, and 10,100 and 7480 ng/mL, respectively, in the 100 mg/kg/day group and the AUC_{0-24} values were 412 and 148 ng·h/mL, respectively, in the 1 mg/kg/day group, 5620 and 2660 ng·h/mL, respectively, in the 10 mg/kg/day group, and 77,200 and 67,500 ng·h/mL, respectively, in the 100 mg/kg/day group. C_{max} and AUC_{0-24} increased with increasing dose and the AUC_{0-24} tended to be higher in females than males, but no apparent gender differences were observed. There was no drug accumulation after repeated dosing.

Pregnant rabbits (n = 5/group) were orally administered tofacitinib for 13 days, from gestation day 7 through gestation day 19, at doses of 10, 30, or 100 mg/kg/day. At the end of dosing (Day 13), the C_{max} values of

[7] Not reportable due to insufficient concentration data.
[8] Not reportable because AUC_{8-24} was greater than 30% of the AUC_{0-24}.
[9] Mean concentrations from all available blood samples collected for the 300 mg/kg/day group

unchanged drug in serum were 610 ± 211, 2490 ± 876, and 8220 ± 2200 ng/mL, respectively, and the AUC_{0-24} values were 1470 ± 264, 6350 ± 1380, and 32,100 ± 7910 ng·h/mL, respectively, and C_{max} and AUC_{0-24} increased with increasing dose.

Monkeys (n = 4/sex/group) were administered tofacitinib orally for 39 weeks as BID at 0.5, 2, or 10 mg/kg/day. On Day 1, the C_{max} values of unchanged drug in serum in females and males were 21.4 ± 6.1 and 20.9 ± 12.9 ng/mL, respectively, in the 0.5 mg/kg/day group, 113 ± 43 and 73.0 ± 31.2 ng/mL, respectively, in the 2 mg/kg/day group, and 370 ± 90 and 508 ± 170 ng/mL, respectively, in the 10 mg/kg/day group and the AUC_{0-24} values were 72.0 ± 21.4 and 76.3 ± 35.0 ng·h/mL, respectively, in the 0.5 mg/kg/day group, 568 ± 75 and 387 ± 102 ng·h/mL, respectively, in the 2 mg/kg/day group, and 2090 ± 360 and 3250 ± 890 ng·h/mL, respectively, in the 10 mg/kg/day group. On Day 254, the C_{max} values in females and males were 22.2 ± 6.4 and 17.6 ± 6.6 ng/mL, respectively, in the 0.5 mg/kg/day group, 132 ± 29 and 82.5 ± 26.5 ng/mL, respectively, in the 2 mg/kg/day group, and 513 ± 116 and 491 ± 90 ng/mL, respectively, in the 10 mg/kg/day group and the AUC_{0-24} values were 91.0 ± 32.2 and 66.3 ± 40.5 ng·h/mL, respectively, in the 0.5 mg/kg/day group, 652 ± 212 and 397 ± 64 ng·h/mL, respectively, in the 2 mg/kg/day group, and 2550 ± 690 and 3140 ± 740 ng·h/mL, respectively, in the 10 mg/kg/day group. C_{max} and AUC_{0-24} increased almost dose-proportionally and no apparent gender differences were observed. There was no drug accumulation after repeated dosing.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution (4.2.2.3.1)

Following oral administration of a single dose of ^{14}C-tofacitinib (10 mg/kg) to male rats (n = 1/timepoint), drug radioequivalents distributed into all tissues by 30 minutes, maximum concentrations of ^{14}C-tofacitinib occurred at 30 minutes for 39 of 54 tissues studied, and the liver, renal medulla, renal cortex, kidneys, ciliary body, uvea, intervertebral discs, exorbital lacrimal gland, and preputial gland had concentrations of radioactivity that were ≥2-fold greater than those observed for blood. Tissue concentrations of ^{14}C-tofacitinib were highest at 1 hour for many tissues and at 12 hours for melanin-containing ocular tissues. Radioactivity was present in the uvea, ciliary body, iris, choroid, liver, intervertebral discs, vessel walls, bladder, kidneys, seminal vesicles, and adrenal glands at 24 hours post-dose and only the vessel walls and melanin-containing ocular tissues had detectable radioactivity at 504 hours post-dose.

3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells (4.2.2.3.2 to 4.2.2.3.4)

In a study of plasma protein binding, tofacitinib was added to plasma at final concentrations of 156, 1250, and 2500 ng/mL. The unbound fraction of tofacitinib was 0.607 to 0.719 for mice, 0.691 to 0.937 for rats, 0.764 to 0.823 for dogs, 0.560 to 0.748 for monkeys, and 0.579 to 0.633 for humans and the unbound fraction of tofacitinib increased in rat plasma with increasing tofacitinib concentration (tofacitinib 156 ng/mL, 0.691 ± 0.006; tofacitinib 1250 ng/mL, 0.913 ± 0.005; tofacitinib 2500 ng/mL, 0.937 ± 0.042). The unbound fractions of tofacitinib in human serum albumin and α1-acid glycoprotein were 0.49 to 0.52 and 1.10 to 1.20, respectively. The blood to plasma concentration ratio of tofacitinib at a concentration of 1 μM (312 ng/mL) was 1.2 for all three species, rat, monkey, and human.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro* studies (4.2.2.4.6, 4.2.2.4.7)

^{14}C-tofacitinib (10 μM) was incubated with human liver microsomes. Unchanged drug, M1, M2, M3, M5, M8, M9, M14, M15, M18, M22, and M25 were detected and unchanged drug (59.2%) was the major component. Ketoconazole (1 μM, a CYP3A inhibitor) inhibited metabolite formation by approximately 70%, furafylline (10 μM, a CYP1A2 inhibitor) inhibited metabolite formation by approximately 10%, and metabolism was inhibited by <10% in the presence of sulfaphenazole (10 μM, a CYP2C9 inhibitor), (+)N-3-benzylnirvanol (10 μM, a CYP2C19 inhibitor), or quinidine (1 μM, a CYP2D6 inhibitor).

Using recombinant human CYP isoforms, CYP isoforms involved in the metabolism of ^{14}C-tofacitinib (10 μM) were identified. The experiments suggest that tofacitinib is mainly metabolized by CYP3A4 and CYP2C19, and CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2D6, and CYP2E1 are also minor contributors.

Based on the above, it has been discussed that CYP3A4 plays a key role in the metabolism of tofacitinib in humans.

3.(ii).A.(3).2) *In vivo* studies (4.2.2.4.1 to 4.2.2.4.5)

Following oral administration of a single dose of ^{14}C-tofacitinib (31 mg/kg) to mice (n = 5/sex/timepoint), M29, M4, unchanged drug, M1/M2, and M14 were detected in plasma up to 8 hours post-dose, M29, M4/M18, unchanged drug, M1/M2, M14, and M9 in urine up to 48 hours post-dose, and M4/M18, M2, unchanged drug, M14, M9, and M1 in feces up to 48 hours post-dose.

Following oral administration of a single dose of ^{14}C-tofacitinib (10 mg/kg) to rats (n = 8/sex), unchanged drug, M1/M2, M21, M4, M14, M29, M13 (observed only in male rats), and M9 were detected in plasma up to 8 hours post-dose, unchanged drug, M1/M2, M4, M14, M13 (observed only in male rats), M6/M21, and M29 in urine up to 24 hours post-dose, and M1/M2, unchanged drug, M14, M9, M6/M21, M13 (observed only in male rats), M4 (observed only in male rats), and one unknown metabolite in feces up to 72 hours post-dose.

Following oral administration of a single dose of ^{14}C-tofacitinib (30 mg/kg) to rabbits (4 females), M20/M29, unchanged drug, M28/M4, M6a, M14a, M26/M2, M14/M6/M19, M1, M25, M18, M11, M13, M8, M9, and three unknown metabolites were detected in plasma up to 4 hours post-dose and M20/M29, M28/M4, M14/M6, unchanged drug, M1, M9, M13, M6a, M11, M19, M18, M26/M2, and two unknown metabolites in urine up to 48 hours post-dose.

Following oral administration of a single dose of ^{14}C-tofacitinib (5 mg/kg) to monkeys (n = 2/sex), unchanged drug, M11/M20/M29, M1/M2, M23, M28, M4, M14, M6, M26, and M9 were detected in plasma up to 2 hours post-dose, M29, M28, unchanged drug, M23, M20, M9, M1/M2, M14, M6, M26, M19 (observed only in female monkeys), M31, and M8 in urine up to 24 hours post-dose, and M4/M18, M6, M1/M2, M9, M14, unchanged drug, M11, M22, M31, M20 (observed only in female monkeys), and one unknown metabolite in feces up to 48 hours post-dose (including one sample collected from 0 to 72 hours post-dose). Following oral administration of a single dose of ^{14}C-tofacitinib (5 mg/kg) to bile duct cannulated male monkeys (n = 2), M25,

M29, M26, M23, M19, M22, M7a, M20, M27, M1, M7b, M14, M24, unchanged drug, and one unknown metabolite were detected in bile up to 24 hours post-dose.

Following oral administration of a single dose of ^{14}C-tofacitinib (50 mg) to humans (6 male subjects), unchanged drug, M1/M2, M20/M11/M29, M4, M14, and M9 were detected in plasma up to 8 hours post-dose, unchanged drug, M9, M11/M29, M4, M1/M2, M14, M20, M8, and M31 in urine up to 24 hours post-dose, and M18/M4, M14, M22, M9, M11, unchanged drug, M2, and one unknown metabolite in feces up to 144 hours post-dose (2 samples collected from 0 to 72 hours post-dose, 1 sample collected from 24 to 96 hours post-dose, 1 sample collected from 24 to 120 hours post-dose, 1 sample collected from 48 to 144 hours post-dose, 1 sample collected from 72 to 144 hours post-dose).

Based on the above metabolism studies, the proposed metabolic pathways for tofacitinib in rats, monkeys, and humans are as shown in Figure 1.

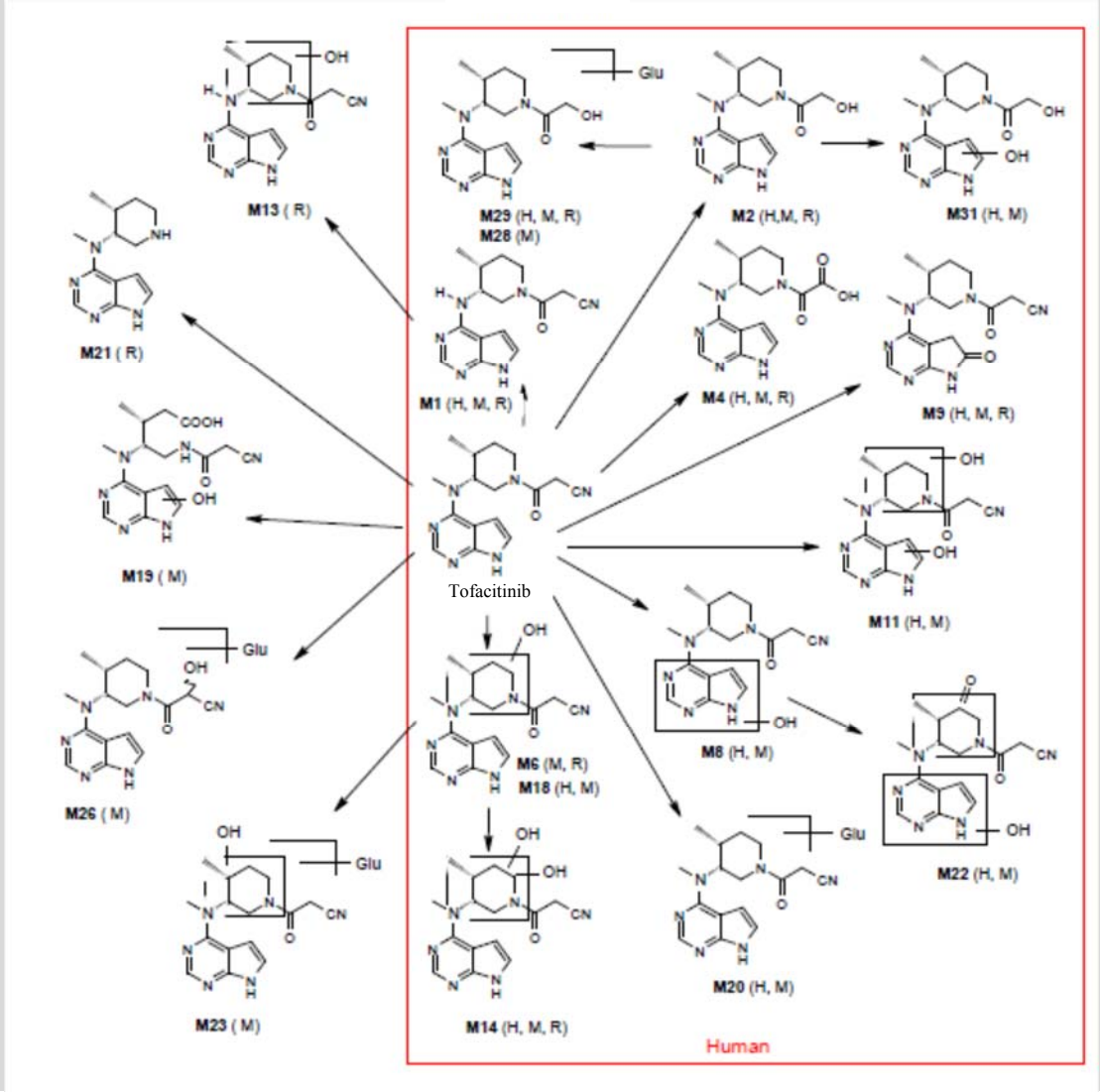


Figure 1. Proposed metabolic pathways for tofacitinib
in human (H), monkey (M), and rat (R) plasma, urine, and feces

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Fecal, urinary, and biliary excretion (4.2.2.4.1, 4.2.2.4.2, 4.2.2.4.4, 4.2.2.4.5, 4.2.2.5.2)

Following oral administration of a single dose of ^{14}C-tofacitinib (31 mg/kg) to mice (n = 6/sex), the total recovery of the dose in the urine over 96 hours (% of administered radioactive dose) was 32.1% in the female and 10.1% in the male and the total recovery of the dose in the feces over 96 hours was 51.2% in the female and 72.1% in the male.

Following oral administration of a single dose of ^{14}C-tofacitinib (10 mg/kg) to rats (n = 3/sex), the total recovery of the dose in the urine over 168 hours was 54.5 ± 2.9% in the female and 48.8 ± 8.1% in the male and the total recovery of the dose in the feces over 168 hours was 42.7 ± 1.6% in the female and 46.6 ± 3.8% in the male.

Following oral administration of a single dose of ^{14}C-tofacitinib (30 mg/kg) to female rabbits (n = 4), the total recovery of the dose over 48 hours was 51.5 ± 16.0% in the urine and 25.0 ± 5.6% in the feces.

Following oral administration of a single dose of ^{14}C-tofacitinib (5 mg/kg) to monkeys (n = 2/sex), the total recovery of the dose in the urine over 168 hours was 55.6% in the female and 42.6% in the male and the total recovery of the dose in the feces over 168 hours was 28.7% in the female and 27.2% in the male. Following oral administration of a single dose of ^{14}C-tofacitinib (5 mg/kg) to bile duct cannulated male monkeys (n = 2), the total recovery of the dose over 48 hours was 44.9% in the urine, 15.4% in the feces, and 25.0% in the bile.

Following oral administration of a single dose of ^{14}C-tofacitinib (50 mg) to humans (6 male subjects), the total recovery of the dose over 192 hours was 80.1 ± 3.6% in the urine and 13.8 ± 1.9% in the feces.

3.(ii).A.(4).2) Lacteal excretion (4.2.2.5.1)

Following oral administration of a single dose of tofacitinib (10 mg/kg) to lactating rats (n = 4/timepoint), the serum and milk concentrations of unchanged drug at 1 hour post-dose in lactating female rats were 1180 ± 360 and 2700 ± 1170 ng/mL, respectively, and the $AUC_{0-\infty}$ values were 3340 and 6960 ng·h/mL, respectively. Tofacitinib was excreted in milk and unchanged drug was present in milk at concentrations that were approximately 2-fold greater than in serum up to 8 hours post-dose.

3.(ii).A.(5) Pharmacokinetic drug interactions

3.(ii).A.(5).1) Enzyme inhibition and enzyme induction (4.2.2.6.1 to 4.2.2.6.3)

Using human liver microsomes, tofacitinib was tested at 0.3, 3.0, and 30 μM for human CYP450 inhibition. The IC_{50} values of tofacitinib for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A were all estimated to be >30 μM (9360 ng/mL).

Using immortalized human hepatocytes (Fa2N-4 cell line) and cryopreserved human hepatocytes, the potential for tofacitinib to induce human CYP450 was investigated. Treatment of immortalized human hepatocytes (Fa2N-4 cell line) with tofacitinib (0.78-100 μM) resulted in a 1.2- to 2.5-fold induction of CYP3A4 mRNA and a 0.74- to 1.2-fold induction of CYP3A4 activity (rifampicin [25 μM] produced a 10-fold induction of CYP3A4 mRNA and a 3.1-fold induction of CYP3A4 activity). Treatment of cryopreserved human hepatocytes with tofacitinib (6.25-100 μM) resulted in a 0.82- to 13-fold induction of CYP3A4 mRNA (a 4.1- to 13-fold induction at ≥25 μM of tofacitinib) and a 1.2- to 1.3-fold induction of CYP3A4 activity (rifampicin [25 μM] produced a 7.7- to 30-fold induction of CYP3A4 mRNA and a 15-fold induction of CYP3A4 activity). Tofacitinib induced a 0.90- to 1.1-fold and a 1.0- to 1.4-fold increase in CYP1A2 activity in Fa2N-4 cells (0.78-100 μM tofacitinib) and cryopreserved human hepatocytes (6.25-100 μM tofacitinib), respectively (omeprazole [50 μM] produced a 6.8- to 36-fold induction of CYP1A2 activity).

3.(ii).A.(5).2) Transporters (4.2.2.6.4 to 4.2.2.6.9)

Studies were carried out in MDCK cells, a Madin-Darby Canine Kidney cell line, expressing MDR1 to identify tofacitinib as a substrate for P-glycoprotein (P-gp). The Efflux Ratios ($P_{appB\rightarrow A}/P_{app\ A\rightarrow B}$) of tofacitinib at 3, 12, and 102 μM were 18.4 ± 0.1, 21.2 ± 0.2, and 10.4 ± 0.1, respectively and the Efflux Ratio was nearly 1 in the presence of P-gp inhibitors, verapamil (100 μM) or ketoconazole (50 μM). Thus, tofacitinib was considered a substrate for P-gp.

Using Caco-2 cell monolayers, P-gp inhibition by tofacitinib (1-1000 μM) was investigated and the IC_{50} was estimated to be 311 μM.

Studies were carried out in MDCK cells expressing breast cancer resistance protein (BCRP) for BCRP substrate evaluation. The Efflux Ratios ($P_{appB\rightarrow A}/P_{appA\rightarrow B}$) for tofacitinib (2 and 20 μM) were 0.94 and 1.05, respectively, and tofacitinib was not considered a substrate of BCRP efflux.

Using HEK293 cells expressing human organic cation transporter (hOCT2) or human hepatic uptake transporter (hOATP1B1 or hOATP1B3), inhibition of each transporter by tofacitinib (1-4100, 0.1-1000, and 0.01-100 μM, respectively) was investigated and the IC_{50} values for hOCT2 and hOATP1B1 inhibition were estimated to be 150 and 55.3 μM, respectively, and tofacitinib was not an inhibitor of hOATP1B3.

3.(ii).B Outline of the review by PMDA

PMDA asked the applicant to discuss the possible causes for gender differences observed at ≤10 mg/kg in rat absorption studies and explain whether gender differences may affect the pharmacokinetics of tofacitinib in humans.

The applicant explained as follows:

Pharmacokinetic studies indicated that the primary clearance mechanism for tofacitinib is CYP450-mediated oxidation and renal clearance of parent drug and that tofacitinib is mainly metabolized by CYP3A4 and CYP2C19 in humans. Therefore, although CYP isoforms involved in the metabolism of tofacitinib in rats were not identified, it is inferred that the metabolism of tofacitinib is primarily mediated by CYP isoforms also in rats. In rats, as female rats have less total P450 compared with male rats, female rats have slower metabolism of drugs in plasma than male rats and it has been reported that the P450 isoforms expressed (CYP2C11 expressed in males, CYP2C12 expressed in females, etc.) and the level of expression (CYP3A2) etc. are different between males and females and there are gender differences in the plasma concentrations of drugs that are primarily metabolized by CYP isoforms (Mugford CA and Kedderis GL. *Drug Metab Rev.* 1998;30:441-498, Imai T. *Drug Delivery System.* 2007;22-1:48-53). Thus, it is considered that gender differences in CYP isoforms that were involved in the metabolism of tofacitinib resulted in the gender differences in exposure. No apparent gender differences were observed at 100 mg/kg/day, which are considered due to saturation of absorption resulting in a non-linear increase in drug plasma concentration at high dose levels in females. In humans, it is known that there are no gender differences in metabolizing enzymes. Although gender was selected as a covariate on CL/F for a population pharmacokinetic analysis (PMAR-00178), it is unlikely that there are changes of ≥23% in CL/F according to gender, and phase I studies also showed no major differences in pharmacokinetic parameters between male and female subjects. Therefore, dose adjustment by gender is not necessary.

PMDA accepted the above response.

In a distribution study, elimination of radioactivity from melanin-containing ocular tissues and vessel walls was slow. PMDA asked the applicant to explain whether findings and adverse events possibly due to drug accumulation in melanin-containing ocular tissues or vessel walls were observed in toxicity studies and clinical studies, respectively.

The applicant explained as follows:
As to melanin-containing ocular tissues, ophthalmoscopy and histopathological examination of the eyes revealed no abnormalities in rat 6-month and monkey 39-week oral toxicity studies. In Japanese and foreign phase III and long-term extension studies in RA patients (data cut-off date of March 29, 2011), the incidence of adverse events involving melanin-containing ocular tissues (iris, ciliary body, choroid) or the retina in subjects treated with tofacitinib was ≤0.2%. The incidence with tofacitinib was not different from that with placebo or adalimumab in a phase III study. Thus, specific adverse events due to drug accumulation in melanin-containing ocular tissues are unlikely to occur.

As to vessel walls, the results of histopathological examinations from rat repeat-dose toxicity studies of up to 6 months duration (single-dose, 14-day, 6-week, and 6-month oral administration studies), a rat carcinogenicity study, and monkey repeat-dose toxicity studies of up to 39 weeks duration (14-day, 4-week, and 39-week oral administration studies) were reviewed. As a result, no findings considered associated with the deposition of tofacitinib in vessel walls, such as vasculitis, perivascular inflammation, thrombus, and hemorrhage, were observed in the aorta or blood vessels in tissues. In 4816 subjects treated with tofacitinib in Japanese and foreign clinical studies in RA patients,[10] vasculitis, phlebitis, thrombophlebitis, superficial thrombophlebitis, rheumatoid vasculitis, and cutaneous vasculitis (1-4 subjects each) as events classified as vasculitis, thrombosis, venous thrombosis, deep vein thrombosis, limb venous thrombosis, coronary artery thrombosis, and subclavian vein thrombosis (9 subjects had deep vein thrombosis, 1-3 subjects each for others) as events classified as thrombosis, and ecchymosis and epistaxis (19 subjects and 21 subjects, respectively) as events classified as haemorrhage were observed. However, events classified as vasculitis, thrombosis, and haemorrhage were generally uncommon and though the events classified as thrombosis were severe in severity, a causal relationship to study drug was denied for most of the events. Therefore, these events are unlikely to be associated with the accumulation of tofacitinib in vessel walls.

PMDA considered that the data have suggested no particular safety concerns due to accumulation of tofacitinib in melanin-containing ocular tissues and vessel walls etc. at present and accepted the above response.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies of tofacitinib conducted include single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and other toxicity studies (*in vitro* and *in vivo* phototoxicity studies). For oral administration studies, doses are expressed as free base equivalents.

[10] A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (1-year cut-off data), A3921045, A3921046, A3921064.

3.(iii).A.(1) Single-dose toxicity (4.2.3.1.1 to 4.2.3.1.3)

Oral and intravenous toxicity studies in rats and an oral toxicity study in monkeys were conducted. The approximate lethal doses in rats by the oral and intravenous routes were determined to be 500 mg/kg and >3 mg/kg, respectively, and the approximate lethal dose in monkeys by the oral route was determined to be >1000 mg/kg. In the rat oral study, the clinical signs included slow respiration, labored respiration, decreased activity, lethargy, and cold to the touch and clinical chemistry and histopathological changes included decreased eosinophils, increased BUN, decreased fibrinogen, increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and glucose, lymphocytolysis in the mesenteric lymph node and a decrease in the number of lymphocytes in the marginal zone of the splenic white pulp, single cell liver necrosis, and lymphocytolysis within the splenic white pulp. In the rat intravenous study, there were no tofacitinib-related findings. In the monkey oral study, emesis and decreased activity were noted.

3.(iii).A.(2) Repeat-dose toxicity

Oral administration studies in rats (6 weeks and 6 months) and monkeys (4 weeks and 39 weeks) were conducted. In both animal species, decreases in circulating lymphocytes, NK cells, and T cells and lymphoid depletion in lymphoid tissues, which were considered attributable to JAK1/3 inhibition by tofacitinib, and decreases in red blood cell parameters and the percent reticulocytes, which were considered attributable to JAK2 inhibition by tofacitinib, were observed. In the monkey 39-week oral study, lymphomas, which were considered associated with immunosuppression, and lymphoid (follicular) hyperplasia in the lymph nodes and spleen were observed. The no observed adverse effect levels (NOAELs) were determined to be 10 mg/kg/day in the 6-month oral study in rats and 2 mg/kg/day in the 39-week oral study in monkeys and there were 4.25-fold and 8.76-fold safety margins in male and female rats, respectively, and there was a 0.51-fold safety margin in male and female monkeys, relative to the $AUC_{0\text{-}24}$ (unbound, 666 ng·h/mL[11]) observed in RA patients following administration of tofacitinib 10 mg twice daily.

3.(iii).A.(2).1) Six-week oral toxicity study in rats (4.2.3.2.3)

Male and female SD rats were orally administered tofacitinib at 0 (vehicle), 1, 10, or 100 mg/kg/day[12] for 6 weeks. Hematologic findings included reductions in eosinophil counts, lymphocyte counts, and red blood cell parameters, etc. at all dose levels and reductions in the percent reticulocytes, etc. at ≥10 mg/kg/day. All parameters tended to recover over the 4-week recovery period and these findings were considered related to the pharmacological effects of tofacitinib and were not considered toxicologically significant. The NOAEL was determined to be 100 mg/kg/day and there were 63-fold and 65-fold safety margins in male and female rats, respectively, relative to the $AUC_{0\text{-}24}$ in RA patients (10 mg BID).

[11] Calculated by multiplying $2\times AUC_{0\text{-}12}$ (545.93 ng·h/mL) after multiple dosing in RA patients in a Japanese phase II study (A3921039) by the unbound fraction (fu) 0.61.

[12] Based on the data from a 14-day exploratory study, 300 mg/kg/day was considered to exceed the maximum tolerated dose and thus, 100 mg/kg/day was used as the high dose in this study.

3.(iii).A.(2).2) Six-month oral toxicity study in rats (4.2.3.2.4)

Male and female SD rats were orally administered tofacitinib at 0 (vehicle), 1, 10, or 100 mg/kg/day for 6 months. Two females in the 1 mg/kg/day group, 1 male and 1 female in the 10 mg/kg/day group, and 1 female in the 100 mg/kg/day group died, of which 3 deaths were considered related to blood collection, but the causes of deaths of the one male in the 10 mg/kg/day group and the one female in the 100 mg/kg/day group were not identified. Clinical signs included salivation and reductions in body weight and body weight gain at 100 mg/kg/day. Hematologic findings included decreases in eosinophil counts and lymphocyte counts etc., as observed in a 6-week oral toxicity study in rats, in females at ≥1 mg/kg/day and males at ≥10 mg/kg/day and reductions in red blood cell parameters, the percent reticulocytes, T cells, B cells, and NK cells at ≥10 mg/kg/day. These findings were all considered related to the pharmacological effects of tofacitinib and were not considered toxicologically significant. Alveolar histiocytosis and interstitial inflammation in the lungs, hepatocellular hypertrophy, and degeneration of the pancreatic islets were observed at 100 mg/kg/day. The NOAEL was determined to be 10 mg/kg/day and there were 4.25-fold and 8.76-fold safety margins in male and female rats, respectively, relative to the $AUC_{0\text{-}24}$ in RA patients (10 mg BID).

3.(iii).A.(2).3) Four-week oral toxicity study in monkeys (4.2.3.2.5)

Male and female cynomolgus monkeys were orally administered tofacitinib at 0 (vehicle), 10, 50, or 100 mg/kg/day[13] for 4 weeks. Three males in the 50 mg/kg/day group were euthanized moribund by Day 26 due to bacterial infection secondary to immunosuppression and all animals in the 100 mg/kg/day group were euthanized by Day 13 due to poor clinical condition. Clinical signs included loose stool and mucoid stool at ≥10 mg/kg/day and decreased activity and decreased body weight with decreased food intake at ≥50 mg/kg/day. Hematological findings included decreases in red blood cell parameters, the percent reticulocytes, T helper cells, cytotoxic T cells, and NK cells etc. in tofacitinib-treated animals. As these findings were all considered related to the pharmacological effects of tofacitinib and were reversible except for decreased NK cells, these changes were not considered toxicologically significant. Animals treated with ≥ 50 mg/kg/day had active bacterial and viral infections secondary to immunosuppression (cynomolgus polyoma virus and herpes virus). The NOAEL was determined to be 10 mg/kg/day and there was a 2.7-fold safety margin relative to the $AUC_{0\text{-}24}$ in RA patients (10 mg BID).

3.(iii).A.(2).4) Thirty-nine-week oral toxicity study in monkeys (4.2.3.2.6)

Male and female cynomolgus monkeys were orally administered tofacitinib at 0 (vehicle), 0.5, 2, or 10 mg/kg/day for 39 weeks. One female in the 10 mg/kg/day group was euthanized on Day 214 due to ulceration/erosions in the stomach, associated with an infiltrative lymphoma that resulted in hemorrhage into the upper gastrointestinal tract. Hematological findings included decreases in red blood cell parameters, T helper cells, cytotoxic T cells, and NK cells etc. in tofacitinib-treated animals and all of these findings were considered related to the pharmacological effects of tofacitinib and were not considered toxicologically significant. Of 8 animals in the 10 mg/kg/day group, 2 animals had B-cell lymphomas and 1 animal had T-cell lymphoma. The two B-cell lymphomas were positive for lymphocryptovirus (LCV), the human EBV-like primate γ-herpesvirus, which are considered similar to lymphomas observed in patients with post-transplant

[13] As mild toxicity was observed at ≥50 mg/kg/day and deaths occurred at ≥200 mg/kg/day in a 14-day exploratory study, 100 mg/kg/day was used as the high dose in this study.

lymphoproliferative disorder (PTLD) resulting from immunosuppression. It has been discussed that the T-cell lymphoma was attributed to a higher sensitivity of T-cells that regulate lymphoma development to tofacitinib in monkeys. Furthermore, lymphoid (follicular) hyperplasia in the lymph nodes and spleen were observed at all dose levels. This was B cell hyperplasia, but was negative for LCV. Thus, this lymphocyte hyperplasia was not considered a precursor of B-cell lymphoma. The NOAEL was determined to be 2 mg/kg/day and there was a 0.51-fold safety margin relative to the $AUC_{0\text{-}24}$ in RA patients (10 mg BID).

3.(iii).A.(3) Genotoxicity (4.2.3.3.1.1 to 4.2.3.3.1.4, 4.2.3.3.2.1)

Genotoxicity studies conducted include a bacterial reverse mutation assay, a gene mutation assay using CHO cells, an *in vitro* chromosome aberration assay with cultured human lymphocytes, *in vivo/in vitro* rat hepatocyte unscheduled DNA synthesis assay, and an *in vivo* rat micronucleus assay. Tofacitinib was tested negative in all assays except for the *in vitro* chromosome aberration assay with cultured human lymphocytes. In the chromosome aberration assay with cultured human lymphocytes, tofacitinib caused an increase in chromosome aberrations in cultured human lymphocytes with metabolic activation. However, as the concentration at which the positive response occurred was higher than the cytotoxic concentration etc., this was not considered toxicologically significant.

3.(iii).A.(4) Carcinogenicity

Oral administration studies in mice (6 months) and rats (2 years) were conducted. While no tofacitinib-related tumors were observed in the 6-month mouse oral study, tofacitinib resulted in increased incidences of benign Leydig cell tumors and benign angiomas in the mesenteric lymph nodes in males and increased incidences of malignant hibernomas and benign thymomas in females in the 2-year rat oral study.

The applicant explained about neoplastic findings observed in rats as follows:
Leydig cell tumors and hibernomas are not relevant or of low relevance to humans, tofacitinib has a wide margin of safety against thymomas, and the incidence of angiomas was increased in the low dose group, but the increased incidence was not dose-dependent and was observed in a single sex and a single species, etc. Therefore, the risk to humans is considered low, but a relevant precaution statement will be included in the package insert.

3.(iii).A.(4).1) Six-month oral carcinogenicity study in mice (4.2.3.4.2.3)

CB6F1/TgrasH2 hemizygous male and female mice were orally administered tofacitinib at 0 (vehicle), 25, 75, or 200 mg/kg/day[14] for 6 months. One female in the 0 mg/kg/day group, 1 female in the 25 mg/kg/day group, 1 female in the 75 mg/kg/day group, and 3 males and 1 female in the 200 mg/kg/day group died during the dosing period. The death of the one female in the 75 mg/kg/day group was attributed to an invasive and metastatic squamous cell carcinoma of cutaneous origin and the causes of other deaths were not identified. As non-neoplastic lesions, focal subphyseal hypocellularity characterized by an increased prominence of adipocytes in the femoral bone marrow and cellular depletion of the red pulp were observed in males at ≥75 mg/kg/day and females at 200 mg/kg/day. The dose at which there were no malignancy findings was

[14] Dose selection was based on the results from a 4-week dose-range-finding study (at 250 mg/kg/day, ataxia, hypoactivity, squinted eyes, irregular respiration, tremors, and recumbency occurred, etc.).

determined to be 200 mg/kg/day and comparison of drug exposure for the mouse with the AUC_{0-24} in RA patients (10 mg BID) resulted in an approximately 17-fold exposure margin.

3.(iii).A.(4).2) Two-year oral carcinogenicity study in rats (4.2.3.4.1.1)

Male and female SD rats were orally administered tofacitinib at 0 (vehicle), 10, 30, 75 (males), or 100 mg/kg/day (females)[15] for 104 weeks. A decreased survival rate in males given 75 mg/kg/day, which was considered attributable to bacterial infection secondary to immunosuppression, was observed. Benign angiomas in the mesenteric lymph nodes in males at 10 mg/kg/day, benign Leydig cell tumors in males at ≥30 mg/kg/day, malignant hibernomas in females at ≥30 mg/kg/day, and benign thymomas in females at 100 mg/kg/day were observed. As non-neoplastic lesions, increased incidences of decreased cellularity of lymphocytes in lymphoid tissues and decreased cellularity in the bone marrow (sternum only), increased incidences of extramedullary hematopoiesis, pigment, and sinusoidal dilatation in the spleen, and increased incidence and severity of alveolar proteinosis and alveolar macrophage infiltrates in the lung were observed in tofacitinib-treated animals. Decreased lymphocyte cellularity was considered attributed to an expected pharmacologic immunomodulatory effect of tofacitinib on the lymphoid/hematopoietic tissues. The dose at which there were no malignancy findings was determined to be 10 mg/kg/day in females and was not identified in males. Comparison of drug exposures at 10, 30, and 75 mg/kg/day in males with the AUC_{0-24} in RA patients (10 mg BID) resulted in approximately 5-, 16-, and 57-fold exposure margins, respectively, and comparison of drug exposures at 10, 30, and 100 mg/kg/day (reduced to 75 mg/kg/day on Day 133) in females with the AUC_{0-24} in RA patients (10 mg BID) resulted in approximately 10-, 39-, and 87-fold exposure margins, respectively.

3.(iii).A.(4).3) Mechanistic studies on carcinogenicity

The following studies were conducted to investigate the mechanism of development of hibernomas and Leydig cell tumors observed in a 2-year oral carcinogenicity study in rats. These studies were not GLP studies.

3.(iii).A.(4).3).(a) Investigative study of the effects of tofacitinib on brown adipose tissue in rats (Reference data 4.2.3.4.3.1)

Female SD rats were orally administered tofacitinib at 0 (vehicle), 10, 30, or 75 mg/kg/day for 2 weeks. As changes in interscapular brown adipose tissue (BAT), decreased phosphorylated STAT5A/B and STAT3 (substrates for JAK activity) at ≥10 mg/kg/day, decreased uncoupling protein-1 (UCP-1) (BAT-specific mitochondrial protein) and cell proliferation at ≥30 mg/kg/day, and increased BAT weight at 75 mg/kg/day were observed. Since these changes occurred at doses associated with a higher incidence of hibernomas in a 2-year oral carcinogenicity study in rats, it has been discussed that hibernoma formation resulted from the inhibition of the JAK/STAT pathway in BAT by tofacitinib.

3.(iii).A.(4).3).(b) Investigative study with rat brown adipocytes (Reference data 4.2.3.4.3.3)

In brown adipocytes (BA) differentiated from the stromal vascular fraction (svf) of interscapular BAT of male and female SD rats, tofacitinib inhibited ovine prolactin (oPRL)-induced increase in phosphorylated

[15] The dose level for the high dose group (at the initiation of treatment) was selected based on the results from a rat 6-month repeated oral dose toxicity study (at 100 mg/kg/day, a reduction in body weight gain in males and hepatocellular hypertrophy in more than one rat, etc. were observed). However, the dose level for high dose females (100 mg/kg/day) was reduced to 75 mg/kg/day on Day 133 due to mortalities related to bacterial infections.

STAT5A/B and basal phosphorylated STAT3 in a concentration-dependent manner.

3.(iii).A.(4).3).(c) Investigative study with rat primary Leydig cells (Reference data 4.2.3.4.3.2)

In primary Leydig cells isolated from the testes of male SD rats, tofacitinib concentration-dependently inhibited oPRL-induced increases in phosphorylated STAT5A/B and luteinizing hormone (LH) receptor mRNA. Thus, it has been discussed that Leydig cell tumors may be attributed to inhibition of prolactin (PRL) signaling via JAK2 within Leydig cells.

3.(iii).A.(5) Reproductive and developmental toxicity

A rat study of fertility and early embryonic development to implantation, embryo-fetal development studies in rats and rabbits, a rat study for effects on pre- and postnatal development, including maternal function, and juvenile rat studies were conducted. In the study of fertility and early embryonic development to implantation, an increase in postimplantation loss, etc. were observed. In the embryo-fetal development studies, tofacitinib was teratogenic in both rats and rabbits. In the study for effects on pre- and postnatal development, including maternal function, the total number of delivered pups and the number of liveborn pups were reduced, etc. In the juvenile rat studies, there were effects on the immune system and hematological parameters, but it has been discussed that these effects were all related to the pharmacological effects of tofacitinib and the findings do not mean that juvenile animals have higher sensitivity to tofacitinib.

3.(iii).A.(5).1) Rat study of fertility and early embryonic development to implantation (4.2.3.5.1.1)

SD rats were orally administered tofacitinib at 0 (vehicle), 1, 10, or 100 mg/kg/day. Females were dosed for 14 days prior to mating and throughout cohabitation period (for a maximum of 2 weeks), continuing through gestation day 7 (Phase 1) and then males were dosed for a minimum of 63 days, beginning 28 days prior to cohabitation (Phase 2). In either Phase 1 or 2, there were no clinical signs or effects on body weight or feed consumption. In Phase 1, at 10 mg/kg/day, there was a slight increase in postimplantation loss. At 100 mg/kg/day, the pregnancy rate was reduced and reductions in the number of corpora lutea, implantation sites, and viable fetuses, an increase in early resorptions, and increases in preimplantation loss and postimplantation loss were observed. In Phase 2, one male in the 100 mg/kg/day group was found dead on dosing day 15 and the cause of death was not identified. There were no effects on male fertility. The NOAELs for paternal and maternal general toxicity were determined to be 10 mg/kg/day and 100 mg/kg/day, respectively, and there were 12-fold and 91-fold safety margins, respectively, relative to the C_{max} (unbound, 75 ng/mL[16]) in RA patients (10 mg BID). The NOAEL for male fertility was determined to be 100 mg/kg/day (a 56-fold safety margin) and the NOAEL for female fertility and early embryonic development was determined to be 1 mg/kg/day (a 3-fold safety margin).

3.(iii).A.(5).2) Embryo-fetal development study in rats (4.2.3.5.2.3 to 4.2.3.5.2.4)

Pregnant SD rats were orally administered tofacitinib from gestation day 6 to gestation day 17 at 0 (vehicle), 1, 10, 30, 100, or 300 mg/kg/day. Decreased activity and reductions in body weight gain and food consumption, etc. were observed in dams at ≥100 mg/kg/day and mortalities occurred at 300 mg/kg/day (13 of 20 dams). As

[16] Calculated by multiplying the multiple-dose C_{max} (122.96 ng/mL) in RA patients in a Japanese phase II study (A3921039) by the unbound fraction (fu) 0.61.

fetal toxicities, total litter loss (7 of 20 dams), increases in early resorptions and postimplantation loss, a reduced number of live fetuses, reduced fetal body weights, and an increase in fetal skeletal malformations were observed at 100 mg/kg/day and all surviving 300 mg/kg/day dams (7 of 20 dams) had total litter loss. The NOAELs for maternal general toxicity and embryo-fetal development were both determined to be 30 mg/kg/day and there was a 38-fold safety margin relative to the $AUC_{0\text{-}24}$ in RA patients (10 mg BID).

3.(iii).A.(5).3) Embryo-fetal development study in rabbits (4.2.3.5.2.5)

Pregnant NZW rabbits were orally administered tofacitinib from gestation day 7 to gestation day 19 at 0 (vehicle), 10, 30, or 100 mg/kg/day. There were no effects on maternal body weight, food consumption, or necropsy findings. Two rabbits in the 100 mg/kg/day group aborted, which was secondary to resorptions and not considered related to the direct effect of tofacitinib on dams. As fetal toxicities, increases in postimplantation loss occurred due to increases in early and late resorptions and consequently, the number of viable fetuses and the gravid uterine weight were reduced at ≥30 mg/kg/day. Fetal examinations revealed increases in midline and tail defects and cardiovascular malformations at ≥30 mg/kg/day, fused skull bones, shortened premaxilla, and small eye sockets correlated with cranio-facial malformations at 30 mg/kg/day, and an increase in fetal visceral variations, reduced fetal body weights, an increased incidence of absent gallbladder, fused sternebrae, increased abnormal vertebrae and ribs, and a reduced number of caudal vertebrae associated with acaudia at 100 mg/kg/day. These findings have previously been reported for other immunosuppressive agents and are considered related to the immunosuppressive activity of tofacitinib. Based on the above results, the NOAEL for maternal general toxicity was determined to be 100 mg/kg/day and there was a 29-fold safety margin relative to the $AUC_{0\text{-}24}$ (bound + unbound,[17] 1092 ng·h/mL) in RA patients (10 mg BID). The NOAEL for embryo-fetal development was determined to be 10 mg/kg/day (a 1.3-fold safety margin).

3.(iii).A.(5).4) Rat study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1)

Pregnant SD rats were orally administered tofacitinib from gestation day 6 through lactation day 20 or gestation day 24 (if a litter was not delivered) at 0 (vehicle), 1, 10, or 50 mg/kg/day. There were no effects on maternal body weight or body weight gain. The total number of delivered pups and the number of liveborn pups, postnatal survival to day 21, and pup body weights were reduced at 50 mg/kg/day. The NOAEL for maternal general toxicity was determined to be 50 mg/kg/day and there was a 54-fold safety margin relative to the $AUC_{0\text{-}24}$ in RA patients (10 mg BID). The NOAEL for viability and growth in the offspring was determined to be 10 mg/kg/day (a 11-fold safety margin).

3.(iii).A.(5).5) Juvenile animal studies

3.(iii).A.(5).5).(a) Juvenile rat study of fertility and early embryonic development to implantation (4.2.3.5.4.2)

Tofacitinib was administered orally at 0 (vehicle), 1, 10, or 100 mg/kg/day to SD rats at 21 days of age for 50 days for males and for 35 days for females. There were no effects on clinical signs, signs of sexual development, estrous cycle, mating index, fertility index, parameters at caesarean section, sperm analysis, or reproductive

[17] As the fu in rabbits was not calculated, the $AUC_{0\text{-}24}$ of bound and unbound tofacitinib was compared. It has been discussed that since there are no major species differences in the fu among humans, mice, and rats etc., the fu in rabbits is also likely to be similar to those in other animal species.

organ weights. The NOAELs for general toxicity, fertility, and early embryonic development were all determined to be 100 mg/kg/day and there were a 86-fold safety margin in males and a 99-fold safety margin in females, relative to the AUC_{0-24} in RA patients (10 mg BID).

3.(iii).A.(5).5).(b) Four-week oral toxicity study in juvenile rats (4.2.3.5.4.3)

Male and female SD rats at 21 days of age were orally administered tofacitinib at 0 (vehicle), 1, 10, or 100 mg/kg/day for 4 weeks. Reduced body weight gains were observed in females at ≥10 mg/kg/day and males at 100 mg/kg/day. Hematological findings included decreases in white blood cell counts, lymphocyte counts, and eosinophil counts in females at ≥1 mg/kg/day and males at ≥10 mg/kg/day, a reduction in basophils and a trend towards a reduction in reticulocytes in males and females at ≥10 mg/kg/day, and a reduction in red blood cell counts at 100 mg/kg/day. Histopathological findings included decreased cellularity in the spleen at ≥10 mg/kg/day and decreased cellularity of lymphocytes in various lymph nodes in females at ≥10 mg/kg/day and males at 100 mg/kg/day. It has been discussed that since all findings were considered attributable to the inhibition of JAK1/3 or JAK2 by tofacitinib, were reversible or tended to be reversed during the recovery period of about 2 months, and occurred at exposure levels similar to or higher than the exposure levels associated with effects in adult rats, these findings do not mean that juvenile rats have higher sensitivity to tofacitinib.

3.(iii).A.(6) Local tolerance

3.(iii).A.(6).1) Murine local lymph node assay (Reference data 4.2.3.6.1)

A local lymph node assay was performed in female CBA/J mice and it was concluded that tofacitinib is not a skin sensitizer.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Phototoxicity

3.(iii).A.(7).1).(a) 3T3 Neutral Red Uptake (NRU) phototoxicity assay (4.2.3.7.7.1)

As tofacitinib has a maximum molar extinction coefficient of 16,005 L/(mol·cm) at 290 nm (pH 7.5) and absorbs light from 290 nm to 700 nm, a phototoxicity assay was performed. Balb/c 3T3 clone 31 mouse fibroblasts were incubated with tofacitinib (0.061-1000 µg/mL) and then irradiated with 5 J/cm^2 ultraviolet A (UVA). Although tofacitinib reduced cellular viability at 1000 µg/mL, as the photo irritation factor (1.00) and the mean photo effect (0.025) were below the cut-off values (2 and 0.1, respectively), it was concluded that tofacitinib has no phototoxic potential *in vitro*.

3.(iii).A.(7).1).(b) Phototoxicity study to determine the effects of one-week oral administration of tofacitinib in Long-Evans pigmented rats (4.2.3.7.7.3)

Tofacitinib did not produce evidence of induced cutaneous or ocular phototoxicity after oral administration of 0 (vehicle), 10, 30, and 100 mg/kg/day for 1 week to Long-Evans pigmented rats followed by a single exposure to simulated sunlight (a xenon lamp) (6.5 kW, 30 minutes).

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Carcinogenicity

Concerning Leydig cell tumors, angiomas, hibernomas, and thymomas observed in a rat 2-year oral carcinogenicity study, PMDA asked the applicant to explain the occurrence of relevant adverse events in clinical studies of tofacitinib and the human relevance of these neoplastic findings.

The applicant explained as follows:

Leydig cell tumor, hibernoma, or thymoma was not reported in clinical studies. As to angiomas, 3 cases of haemangioma of liver and 1 case of spinal haemangioma were reported, of which a causal relationship to tofacitinib could not be denied for the 1 case of haemangioma of liver. However, in rats, all of the angiomas occurred in the mesenteric lymph nodes, i.e. in a different location from those of the haemangiomas reported in the clinical studies. The angiomas observed in rats were benign and the increased incidence was not dose-dependent and was observed in a single sex. Taking account of these findings etc., the risk to humans is considered low.

In a monkey 39-week oral toxicity study (a monkey 39-week toxicity study), 3 of 8 monkeys had lymphomas. Also in clinical studies, lymphomas have been observed in RA patients treated with tofacitinib [see "4.(iii) Summary of clinical efficacy and safety"]. PMDA asked the applicant to explain the human relevance of this finding.

The applicant explained as follows:

Of the 3 lymphomas observed in the monkey 39-week toxicity study, 2 were identified as B cell origin and were positive for LCV. Meanwhile, of 7 lymphomas observed in tofacitinib-treated subjects in RA clinical studies, 6 were negative or false-positive for EBV. Thus, it is considered that the mechanism of development of lymphoma was different between monkeys and humans. The remaining one monkey had T-cell lymphoma, which was considered a different type of lymphoma from the above two cases. Although T-cell lymphoma occurs occasionally in immunosuppressed patients, e.g. post-transplant lymphoproliferative disorder (PTLD) (Swerdlow SH, et al. *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. 4th ed.* Lyon, France: International Agency for Research on Cancer 2008;343-349, Haga H, et al. *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues.* 539-548), in such cases, the mechanism of development of lymphoma unrelated to EBV infection is not defined. However, tofacitinib treatment resulted in reductions in circulating T cells (CD4+, CD8+) in the monkey 39-week toxicity study while tofacitinib had no effect on T-cell subsets even at similar or higher exposure levels in humans [see "4.(ii) Summary of clinical pharmacology studies"], which indicate a higher sensitivity of T cells to tofacitinib in monkeys than in humans. Thus, it is inferred that the risk of T-cell lymphoma is lower in humans than in monkeys.

Lymphomas and PTLD associated with LCV were observed in renal-transplanted monkeys on multiple immunosuppressive agents (McInnes EF, et al. *Transplantation.* 2002;73:44-52, Schmidtko J, et al. *Transplantation*. 2002;73:1431-1439) and the development of lymphoma in monkeys is considered to result from over-immunosuppression by the use of immunosuppressive drugs during viral infection or by simian immunodeficiency virus infection (Weaver JL. *Toxicol Pathol.* 2012;40:267-271). In clinical studies of tofacitinib in renal transplant patients, tofacitinib was administered in combination with multiple immunosuppressive drugs and lymphoma was observed in 5 patients (non-Hodgkin's lymphoma [4 patients], Hodgkin's lymphoma [1 patient]) and all of these patients were EBV-positive, suggesting that lymphomas resulting from EBV reactivation from over-immunosuppression are relevant to humans.

PMDA asked the applicant to explain the possibility that lymphomas were related to M11 (oxidation of the piperidine and pyrrolopyrimidine rings) and M20 (the glucuronide of tofacitinib), which are metabolites that are detected in humans and monkeys, but not in rats or mice.

The applicant explained as follows:
The proposed chemical structures of M11 and M20 were evaluated using an *in silico* system for the prediction of toxicity based on the database of known toxicological structure-activity relationships, DEREK (Deductive Estimation of Risk from Existing Knowledge, Lhasa, Ltd). As a result, the risk of mutagenicity was not suggested. Therefore, these metabolites are unlikely to be involved in the development of lymphoma.

PMDA accepts the above response from a toxicological point of view, but considers as follows:
As the incidence of malignancies tended to be higher with tofacitinib compared with placebo in clinical studies [see "4.(iii) Summary of clinical efficacy and safety"], the risk of malignancy associated with tofacitinib should be carefully assessed based on clinical study data. Especially, a special attention should be paid to the possible development of lymphoma when high-dose tofacitinib is administered or tofacitinib is used for a long period of time or in combination with immunosuppressive drugs, etc. and the package insert should contain an adequate warning statement because, although the relationship between lymphomas observed in RA patients and tofacitinib is not clear at present, the risk of lymphoma associated with tofacitinib can not be ruled out, in view of its immunosuppressive activity; lymphomas considered associated with over-immunosuppression have been observed in renal transplant patients; and lymphomas occurred relatively early, by Week 39, and dose-dependently in monkeys.

3.(iii).B.(2) Teratogenic findings
Since tofacitinib was teratogenic in both rat and rabbit reproductive and developmental toxicity studies, PMDA requested that the following statements should be included in the draft package insert: tofacitinib is contraindicated in pregnant women or women who may possibly be pregnant; and women of childbearing potential should be advised to avoid becoming pregnant during and for a period of time after treatment, etc.

The applicant accepted it.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

As the evaluation data, the results from absolute bioavailability (5.3.1.1.1, A3921077), bioequivalence (5.3.1.2.2, A3921075; 5.3.1.2.4, A3921135), and food effect (5.3.1.2.3, A3921076) studies in foreign subjects were submitted. As the reference data, the results from a food effect study in foreign subjects (5.3.1.2.1, A3921005), etc. were submitted. Plasma tofacitinib concentrations were determined by liquid chromatography/tandem mass spectrometry (LC/MS/MS) (Lower limit of quantitation, 0.100-1.00 ng/mL). Unless otherwise specified, the data and pharmacokinetic parameters are expressed as the mean or the mean ± SD.

4.(i).A.(1) Absolute bioavailability (5.3.1.1.1, Study A3921077 [July to August 2010])

A randomized, open-label, 2-treatment, 2-period, crossover study in foreign healthy adult subjects (n = 12) was conducted to estimate the absolute oral bioavailability of tofacitinib. Pharmacokinetic parameters following administration of a single oral or intravenous dose of 10 mg of tofacitinib were as shown in Table 4 and the absolute bioavailability of tofacitinib following oral administration (the ratio of adjusted geometric means [90% confidence interval (CI)]) was 74.14 [70.32, 78.16]%.

Table 4. Pharmacokinetic parameters following oral or intravenous administration of 10 mg of tofacitinib to foreign healthy adult subjects

	n	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	AUC_{inf} (ng·hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	CL (mL/min)	Vss (L)
Oral administration	12	114.3 (19)	297.6 (23)	299.7 (23)	0.584 (0.333-0.667)	3.558 (10)	-	-
Intravenous administration	12	182.7 (25)	402.0 (19)	404.2 (19)	0.467 (0.333-0.483)	3.523 (9)	412.3 (19)	87.08 (16)

Geometric mean (%CV), Median (range) for t_{max}, Arithmetic mean (%CV) for $t_{1/2}$

C_{max}: maximum plasma concentration, AUC_{last}: area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, AUC_{inf}: area under the plasma concentration-time curve from zero to infinity, t_{max}: time of occurrence of C_{max}, $t_{1/2}$: terminal half-life, CL: clearance, Vss: volume of distribution at steady state

4.(i).A.(2) Bioequivalence studies

4.(i).A.(2).1) Bioequivalence study (5.3.1.2.2, Study A3921075 [September 2010])

A randomized, open-label, 3-treatment, 3-period, crossover, bioequivalence study in foreign healthy adult subjects (n = 24) was conducted to compare the late phase II tablet formulation (10 mg tofacitinib [two 5 mg tablets]), the phase III tablet formulation (10 mg tofacitinib [two 5 mg tablets]), and the to-be-marketed tablet formulation (10 mg tofacitinib [one 10 mg tablet]) of tofacitinib. The adjusted geometric mean ratios of pharmacokinetic parameters [90% CI] were as follows: the C_{max}, AUC_{last}, and AUC_{inf} ratios of the to-be-marketed tablet formation versus the late phase II tablet formulation were 93.88 [85.31, 103.32]%, 98.98 [96.15, 101.89]%, and 98.97 [96.13, 101.88]%, respectively, the C_{max}, AUC_{last}, and AUC_{inf} ratios of the to-be-marketed tablet formulation versus the phase III tablet formulation were 105.20 [95.57, 115.80]%, 99.52 [96.68, 102.45]%, and 99.54 [96.69, 102.47]%, respectively, and the C_{max}, AUC_{last}, and AUC_{inf} ratios of the phase III tablet formulation versus the late phase II tablet formulation were 89.24 [81.20, 98.08]%, 99.45 [96.65, 102.34]%, and 99.43 [96.62, 102.31]%, respectively, suggesting that these three formulations are bioequivalent.

4.(i).A.(2).2) Bioequivalence study (5.3.1.2.4, Study A3921135 [February to March 2011])

A randomized, open-label, 2-period crossover, bioequivalence study in foreign healthy adult subjects (n = 24) was conducted to compare different strengths of the late phase II tablet formulation (one 5 mg tablet versus five 1 mg tablets). The adjusted geometric mean ratios of pharmacokinetic parameters for one 5 mg tablet versus five 1 mg tablets [90% CI] were as follows: The C_{max}, AUC_{last}, AUC_t, and AUC_{inf} ratios were 94.63 [81.52, 109.85]%, 99.43 [96.36, 102.59]%, 99.30 [96.19, 102.52]%, and 99.38 [96.28, 102.58]%, respectively, suggesting that one 5 mg tablet is bioequivalent to five 1 mg tablets.

4.(i).A.(3) Food effect

4.(i).A.(3).1) Foreign studies

4.(i).A.(3).1).(a) Food effect in foreign subjects (5.3.1.2.3, Study A3921076 [September 2010])

A randomized, open-label, 2-period crossover study in foreign healthy adult subjects (n = 16) was conducted to evaluate the effect of food (a high-fat meal) on the pharmacokinetics of a single 10 mg oral dose of tofacitinib. The adjusted geometric mean ratios of pharmacokinetic parameters for fed versus fasted conditions [90% CI] were 68.18 [58.39, 79.61]% for C_{max}, 105.87 [102.44, 109.41]% for AUC_{last}, and 106.03 [102.62, 109.56]% for AUC_{inf} and food increased the AUC_{inf} by about 6%, but decreased the C_{max} by about 32%, and the t_{max} (median [range]) increased from 0.50 (0.48-2.00) to 2.0 (0.50-4.0) hours.

4.(i).A.(3).1).(b) Food effect in foreign subjects (5.3.1.2.1, Study A3921005 [January to April 2003]) (Reference data)

A randomized, open-label, 3-period crossover study in foreign healthy adult subjects (n = 12) was conducted to evaluate the relative bioavailability of a single 50 mg oral dose of tofacitinib given as the early phase II tablets (two 20 mg tablets and two 5 mg tablets) or the oral powder for constitution (OPC) and the effect of food (a high-fat meal) on the pharmacokinetics of a single 50 mg oral dose of tofacitinib given as the early phase II tablets. The adjusted geometric mean ratios of pharmacokinetic parameters for the tablet formulation versus OPC [90% CI] were 76.41 [69.95, 83.47]% for C_{max} and 96.32 [92.33, 100.47]% for AUC_{inf}. The adjusted geometric mean ratios of pharmacokinetic parameters of tofacitinib given as the early phase II tablets for fed versus fasted conditions [90% CI] were 74.25 [67.97, 81.11]% for C_{max} and 114.96 [110.20, 119.91]% for AUC_{inf} and food increased the AUC_{inf} by about 15%, but the C_{max} was reduced by about 26% and the t_{max} (median [range]) increased from 1 (0.5-2) to 2 (0.5-4) hours.

4.(i).B Outline of the review by PMDA

4.(i).B.(1) Food effect

Concerning the effect of food on the pharmacokinetics of tofacitinib, foreign clinical studies showed a trend towards decrease in C_{max} following coadministration of food. PMDA asked the applicant to explain the possibility that food has a clinically significant effect on the efficacy and safety of tofacitinib in Japanese patients.

The applicant explained as follows:

In a pharmacokinetic/pharmacodynamic modeling study using data from non-clinical pharmacology studies [see "3.(i) Summary of pharmacology studies"], the total daily exposure ($AUC_{0\text{-}24}$) or the duration of blood

concentrations above the IC_{50} for JAK1/3 was a better predictor of efficacy of tofacitinib QD or BID than the C_{max} or C_{min}. In a foreign food effect study in healthy adult subjects (A3921076), food had no significant effect on the AUC and when the dose was normalized to 5 mg, the duration of blood concentrations above the IC_{50} for JAK1/3 was about 3.5 hours under fed conditions, which was similar to 3 hours under fasted conditions. Based on the above, decrease in the C_{max} resulting from coadministration with food has no clinically significant effect on the efficacy of tofacitinib.

Regarding safety, a logistic regression analysis of 4 Japanese and foreign phase II studies (A3921025, A3921035, A3921039, A3921040) was performed to examine the relationship between C_{max} and the incidence of adverse events. The slope of the regression curve around the value of thegeometric mean $C_{max,ss}$ of tofacitinib (5 mg BID) (58.6 ng/mL) is gentle and therefore it is considered that an about 30% difference in the C_{max} between fed and fasted conditions does not significantly affect the incidence of adverse events.

In conclusion, tofacitinib can be administered with or without food.

PMDA accepted the above response and concluded that there is no need to specify the timing of tofacitinib administration relative to meals.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

As the evaluation data, the results from a pharmacokinetic study in Japanese and foreign healthy adult subjects (5.3.3.1.3, A3921036), a single oral dose study in foreign healthy adult subjects (5.3.3.1.1, A3921002), a mass balance study in foreign healthy adult subjects (5.3.3.1.2, A3921010), population pharmacokinetic analysis (5.3.3.5.1, PMAR-00178), intrinsic factor pharmacokinetic studies in foreign subjects (5.3.3.3.1, A3921004; 5.3.3.3.2, A3921006; 5.3.3.3.3, A3921015), drug-drug interaction studies in foreign subjects (5.3.3.2.2, A3921013; 5.3.3.4.1, A3921014; 5.3.3.4.2, A3921020; 5.3.3.4.3, A3921054; 5.3.3.4.4, A3921056; 5.3.3.4.5, A3921059; 5.3.3.4.6, A3921071), and pharmacodynamic studies in foreign subjects (5.3.4.1.1, A3921028; 5.3.4.1.2, A3921033; 5.3.4.2.1, A3921109), etc. were submitted.

4.(ii).A.(1) Healthy adult subject studies

4.(ii).A.(1).1) Pharmacokinetic study in Japanese and foreign healthy adult subjects (5.3.3.1.3, Study A3921036 [May to July 2007])

A placebo-controlled, randomized, double-blind, dose escalation study in Japanese and foreign healthy adult subjects (12 Japanese subjects, 6 Caucasian subjects) was conducted to investigate the single and multiple oral dose pharmacokinetics of tofacitinib.

Pharmacokinetic parameters in Japanese and foreign healthy adult subjects following administration of a single oral dose of 1, 5, or 30 mg of tofacitinib were as shown in Table 5. The C_{max} and AUC increased in a dose-dependent manner and there were no major differences in the pharmacokinetics of tofacitinib between the two populations. The mean percent of administered dose excreted unchanged in urine up to 24 hours post-dose was 20.4% to 22.5% in Japanese subjects and 19.8% to 21.2% in foreign subjects and ≥90% of the total amount of

parent drug excreted in urine was excreted within 12 hours post-dose.

Table 5. Pharmacokinetic parameters of tofacitinib following administration of single oral doses in Japanese and foreign healthy adult subjects

	Dose	n	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	AUC_{inf} (ng·hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	CL_R (mL/min)
Japanese subjects	1 mg	6	7.32 (14)	21.4 (29)	22.0 (28)	0.75 (0.50-2.00)	1.96 (1.69-2.40)	162 (27)
	5 mg	6	41.3 (35)	110 (22)	111 (22)	0.50 (0.50-1.00)	2.49 (2.06-3.60)	134[a] (25)
	30 mg	6	315 (25)	752 (26)	754 (26)	0.50 (0.50-1.00)	3.14 (2.56-3.79)	148 (27)
Foreign subjects	1 mg	6	7.36 (22)	22.2 (11)	22.8 (11)	0.75 (0.50-1.00)	2.14 (1.80-2.34)	160[a] (11)
	5 mg	6	34.9 (27)	118 (14)	119 (14)	0.50 (0.50-2.00)	2.85 (2.13-3.93)	136[a] (29)
	30 mg	6	265 (18)	785 (16)	788 (16)	0.50 (0.50-1.00)	3.50 (2.89-3.81)	124 (24)

Geometric mean (%CV), Median (range) for t_{max}, Mean (range) for $t_{1/2}$ a) n = 5

Following administration of a single oral dose of 15 mg of tofacitinib and multiple oral doses of 15 mg twice daily for 5 days (separated by 2-day washout period) in Japanese healthy adult subjects (n = 6), a steady-state was achieved within 24 hours after initiating multiple dosing and the single- and multiple-dose (Day 5) pharmacokinetic parameters were as follows: the C_{max} values (geometric mean [%CV]) were 141 (34) and 136 (32) ng/mL, respectively, the AUC_{0-12} values (geometric mean [%CV]) were 387 (32) and 445 (25) ng·hr/mL, respectively, the t_{max} values (median [range]) were 0.75 (0.50-1.00) and 0.75 (0.50-1.00) hours, respectively, and the $t_{1/2}$ values (mean [range]) were 3.14 (2.36-4.06) and 3.28 (2.58-3.97) hours, respectively. The ratio of the AUC_{0-12} on Day 5 to the AUC_{0-12} after a single dose was 1.15.

4.(ii).A.(1).2) Single oral dose study in foreign healthy adult subjects (5.3.3.1.1, Study A3921002 [April to August 2002])

A placebo-controlled, double-blind, dose escalation study in foreign healthy adult subjects (n = 5-9/group) was conducted to evaluate the pharmacokinetics of single oral doses of tofacitinib (OPC). Pharmacokinetic parameters following administration of a single oral dose of 0.1, 0.3, 1, 3, 10, 30, 60, or 100 mg of tofacitinib were as shown in Table 6 and the C_{max} and AUC increased in a dose-dependent manner.

Table 6. Pharmacokinetic parameters following administration of a single oral dose of tofacitinib to foreign healthy adult subjects

Dose	n	C_{max} (ng/mL)	AUC_{last} (ng·hr/mL)	AUC_{inf} (ng·hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
0.1 mg	5	1.27 ± 0.08	0.16 ± 0.01	-	0.5 (0.5-0.5)	-
0.3 mg	8	2.65 ± 0.62	3.91 ± 2.07	-	0.5 (0.5-1)	-
1 mg	8	10.5 ± 2.28	19.2 ± 6.54	-	0.5 (0.5-1)	-
3 mg	8	21.8 ± 3.04	69.5 ± 13.4	75.5 ± 14	0.5 (0.5-1)	2.31 ± 0.348
10 mg	8	88 ± 10.2	283 ± 80.3	289 ± 81.5	0.5 (0.25-1)	2.61 ± 0.633
30 mg	9	240 ± 44.5	933 ± 176	938 ± 175	0.5 (0.25-2)	2.72 ± 0.576
60 mg	8	408 ± 97.7	1710 ± 435	1720 ± 438	1 (0.5-1)	2.68 ± 0.555
100 mg	7	638 ± 118	2980 ± 709	2990 ± 716	0.5 (0.5-2)	3.07 ± 0.571

Mean ± SD, Median (range) for t_{max}

4.(ii).A.(1).3) Mass balance and metabolic profile in humans (5.3.3.1.2, Study A3921010 [March to April 2004])

An open-label study in foreign healthy adult subjects (n = 6) was conducted to evaluate the mass balance and metabolic profile of tofacitinib. Following administration of a single 50 mg oral dose of ^{14}C-tofacitinib (OPC), the pharmacokinetic parameters of tofacitinib were as follows: the C_{max} was 397 ± 62 ng/mL, the AUC_{inf} was 1680 ± 380 ng·hr/mL, and the apparent terminal half-life ($t_{1/2}$) was 3.15 ± 0.56 hours and the pharmacokinetic parameters of total radioactivity were as follows: the C_{max} was 611 ± 69 ng eq./mL, the AUC_{inf} was 3440 ± 798 ng eq.·hr/mL, and the $t_{1/2}$ was 3.18 ± 0.48 hours.

The mean cumulative total, urinary, and fecal recoveries of administered radioactivity (% of dose) over 192 hours after dosing were 93.9 ± 3.6%, 80.1 ± 3.6%, and 13.8 ± 1.9%, respectively, and approximately 30% of the administered radioactivity was excreted unchanged in the urine.

The primary metabolic pathways of tofacitinib 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 N-demethylation to form M1.

4.(ii).A.(2) Population pharmacokinetic analysis (5.3.3.5.1, PMAR-00178)

The population pharmacokinetic analysis (NONMEM Version 7.1.2) considered phase II studies in Japanese and foreign RA patients (A3921019, A3921025, A3921035, A3921039, A3921040) and included 6039 observations from 1070 patients. In the clinical studies, doses ranged from 1 to 30 mg BID and 20 mg QD. The base pharmacokinetic model was a linear one-compartment model parameterized in terms of apparent oral clearance (CL/F), apparent volume of distribution (V/F), and zero-order absorption duration (D1).

The covariates evaluated in the model[18] were baseline age, body weight, gender, race, and creatinine clearance (CLcr) and study (A3921025) for CL/F and body weight and age for V/F. The typical estimates [90% CI] of population pharmacokinetic parameters for "a reference patient" (Caucasian, male, 70 kg, 55 years, CLcr ≥80 mL/min, non-study A3921025) were 18.4 [16.1, 22.7] L/h, 96.0 [92.8, 99.6] L, and 0.352 [0.267, 0.410] hours for CL/F, V/F, and D1, respectively. Inter-individual variability estimates for CL/F and V/F (%CV) were 26.6% and 26.0%, respectively, and inter-occasion variability in F was 23.0%. Residual variability in pre-dose (trough) and non-pre-dose concentrations were estimated to be 64.1% and 34.4%, respectively.

There should be changes of less than 28% in CL/F according to covariates of body weight, age, gender, and race. Relative to "a reference patient," a patient with CLcr 40 mL/min was estimated to have 23% lower CL/F, patients with body weight 40 kg and 140 kg were estimated to have approximately 39% lower V/F and 84% higher V/F, respectively, and a patient aged 80 years was estimated to have 11% lower V/F. C_{max} for a 40 kg patient aged 55 years was estimated to be 50% higher and for a 140 kg patient aged 55 years 25% lower than that of a 70 kg patient and C_{max} and C_{min} for a 40 kg patient aged 80 years were estimated to be 67% higher and 71% lower than those of a 70 kg patient aged 55 years, respectively.

[18] For the selection of covariates in PPK model building, as estimation rather than test of covariate effects was focused upon, it was planned to evaluate potential covariates based on prior knowledge and construct a full model, avoiding highly correlated covariates or multicollinearity.

4.(ii).A.(3) Intrinsic factor pharmacokinetic studies

4.(ii).A.(3).1) Pharmacokinetics in subjects undergoing hemodialysis (5.3.3.3.1, Study A3921004 [February to June 2003])

An open-label study in foreign subjects receiving three hemodialysis sessions per week for ≥6 weeks (n = 11-12/Period) was conducted to evaluate the pharmacokinetics of tofacitinib. Pharmacokinetic parameters following administration of a single 10 mg oral dose of tofacitinib 1 to 2 hours after completion of hemodialysis (Period 1) were as follows: the C_{max} was 106 ± 23.9 ng/mL, the AUC_{inf} was 396 ± 158 ng·hr/mL, the t_{max} (median [range]) was 0.5 (0.5-0.5) hours, the $t_{1/2}$ was 3.46 ± 1.18 hours, and the CL_{po} was 501 ± 243 mL/min.

The pharmacokinetic data (plasma and dialysate) from the first 2 subjects in Period 1 were analyzed, which suggested extensive non-renal clearance and the degree to which tofacitinib was dialyzable could not be assessed. Thus, 10 mg of tofacitinib was administered as a single oral dose approximately 4 hours prior to hemodialysis (Period 2) to determine the dialyzer clearance of tofacitinib. The dialyzer clearance of tofacitinib was 318 ± 132 mL/min (blood flow entering dialyzer, 423 ± 113 mL/min) and it remained consistent within each subject, but there was considerable inter-subject variability (range, 174-527 mL/min).

4.(ii).A.(3).2) Pharmacokinetics in subjects with impaired renal function (5.3.3.3.2, Study A3921006 [October 2003 to March 2004])

An open-label, parallel-group, comparative study in foreign subjects with impaired renal function (n = 6/group) was conducted to evaluate the pharmacokinetics of tofacitinib. Pharmacokinetic parameters by degree of renal impairment (classified into normal function, mild impairment, moderate impairment, and severe impairment by CLcr estimated using Cockcroft-Gault method) following administration of a single 10 mg oral dose of tofacitinib were as shown in Table 7. Although the C_{max} was comparable regardless of the degree of renal impairment, the AUC_{inf} increased, the renal clearance (CL_R) decreased, and the terminal half-life increased with decline in renal function. The AUC_{inf} was statistically significantly greater in the moderate and severe renal impairment groups compared with the normal renal function group. Correlation coefficient between the natural log-transformed AUC_{inf} and CLcr was 0.67.

Table 7. Pharmacokinetic parameters following a single 10 mg oral dose of tofacitinib in subjects with impaired renal function

		n	C_{max} (ng/mL)	AUC_{inf} (ng·hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	CL_R (mL/min)
Normal	(CLcr >80)	6	94.2 ± 25.3	268 ± 71.5	0.75 (0.50-1.50)	2.37 ± 0.363	113 ± 16.2
Mild	(CLcr >50 and ≤80)	6	87.3 ± 23.2	370 ± 109	1.00 (0.50-1.50)	2.83 ± 0.857	84.7 ± 28.7
Moderate	(CLcr ≥30 and ≤50)	6	104 ± 47.5	396 ± 154	0.75 (0.50-2.00)	2.88 ± 0.653	27.4 ± 15.9
Severe	(CLcr <30)	6	111 ± 28.6	615 ± 214	0.75 (0.50-1.50)	3.77 ± 0.480	19.9 ± 7.52

Mean ± SD, Median (range) for t_{max}

Based on the above results, the applicant explained as follows:

Tofacitinib dose should not exceed 5 mg twice daily in patients with severe renal impairment due to the potential for high systemic exposures. The AUC in subjects with severe renal impairment (615 ± 214 ng·hr/mL, A3921006) was higher than the AUC in subjects undergoing hemodialysis (396 ± 158 ng·hr/mL, A3921004) and the increase was more than accounted for by the contribution of renal clearance to total clearance

(approximately 30%) and though its cause is unknown, the effects of uremia on enzymes and transporters may have partially been corrected by hemodialysis (Dreisbach AW. *Clin Pharmacol Ther.* 2009;86:553-556).

4.(ii).A.(3).3) Pharmacokinetics in subjects with hepatic impairment (5.3.3.3.3, Study A3921015 [November 2009 to January 2010])

An open-label study in foreign subjects with hepatic impairment (n = 6/group) was conducted to evaluate the pharmacokinetics of tofacitinib. Pharmacokinetic parameters following administration of a single 10 mg oral dose of tofacitinib in subjects with mild (Child-Pugh score of 5-6) or moderate (Child-Pugh score of 7-9) hepatic impairment and healthy adult subjects (normal hepatic function) were as shown in Table 8. Subjects with moderate hepatic impairment had 49% increase in C_{max}, 65% increase in AUC_{inf}, and prolonged $t_{1/2}$ compared with subjects with normal hepatic function.

Table 8. Pharmacokinetic parameters following a single 10 mg oral dose of tofacitinib in subjects with hepatic impairment

	n	C_{max} (ng/mL)	AUC_{inf} (ng·hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)
Normal	6	60.5 (23)	355 (23)	3.0 (1.0-6.0)	4.09 (23)
Mild	6	60.1 (27)	366 (15)	2.5 (0.5-4.0)	4.37 (9)
Moderate	6	89.9 (33)	584 (45)	0.8 (0.5-2.0)	5.41 (20)

Geometric mean (%CV), Median (range) for t_{max}, Arithmetic mean (%CV) for $t_{1/2}$

Based on the above results, the applicant explained as follows:

Tofacitinib dose should not exceed 5 mg twice daily in patients with moderate hepatic impairment due to the potential for high systemic exposures. Patients with severe hepatic impairment were excluded from tofacitinib clinical studies because hepatic metabolism constitutes as much as about 70% of the total clearance of tofacitinib and tofacitinib is not recommended in patients with severe hepatic impairment.

4.(ii).A.(4) Drug-drug interaction studies

4.(ii).A.(4).1) MTX (5.3.3.2.2, Study A3921013 [April 2005 to June 2006])

A study in foreign RA patients who were receiving a stable MTX dose (15-25 mg/week) for a minimum of 28 days (n = 12) was conducted to estimate the effects of MTX on the pharmacokinetics of tofacitinib and the effects of tofacitinib on the pharmacokinetics of MTX. An individualized single dose of MTX was administered on Day 1, 30 mg of tofacitinib was orally administered twice daily on Days 3 to 6, and 30 mg of tofacitinib and a single oral dose of MTX were administered on Day 7. The geometric mean ratios of pharmacokinetic parameters for comparison of tofacitinib given with MTX vs. tofacitinib or MTX given alone [90% CI] were as follows: the C_{max} and AUC_{0-12} ratios of tofacitinib were 102.71 [93.79, 112.47]% and 103.06 [99.00, 107.29]%, respectively, and the C_{max} and AUC_{0-24} ratios of MTX were 87.25 [76.03, 100.12]% and 89.53 [77.38, 103.57]%, respectively, and coadministration with tofacitinib decreased the AUC of MTX by 10% and the C_{max} of MTX by 13%.

4.(ii).A.(4).2) Fluconazole (5.3.3.4.1, Study A3921014 [November to December 2005])

A study in foreign healthy adult subjects (n = 12) was conducted to estimate the effect of fluconazole on the pharmacokinetics of tofacitinib. Subjects received a single 30 mg oral dose of tofacitinib (alone), underwent a 3-day washout period, and received a loading dose of oral fluconazole (400 mg), an inhibitor of CYP3A4 and CYP2C19, on Day 1 and maintenance doses (200 mg QD) on Days 2 to 7 with a single 30 mg oral dose of

tofacitinib (coadministration) on Day 5. The adjusted geometric mean ratios of pharmacokinetic parameters of tofacitinib for comparison of tofacitinib given with fluconazole vs. tofacitinib given alone [90% CI] were as follows: the C_{max} ratio was 126.74 [111.82, 143.66]% and the AUC_{inf} ratio was 179.26 [163.81, 196.16]%. The $t_{1/2}$ increased from 2.97 ± 0.59 to 4.00 ± 0.70 hours and the CL_R decreased from 7.57 ± 2.97 to 5.24 ± 2.69 L/hr.

4.(ii).A.(4).3) Tacrolimus and cyclosporine (5.3.3.4.2, Study A3921020 [June to August 2009])

A study in foreign healthy adult subjects (n = 12/Cohort) was conducted to estimate the effect of tacrolimus and cyclosporine on the pharmacokinetics of tofacitinib. Subjects received a single 10 mg oral dose of tofacitinib (alone) and started with tacrolimus or cyclosporine as an immunosuppressant/CYP3A4 inhibitor on the following day. In Cohort A, 5 mg of tacrolimus was orally administered twice daily on Days 1 to 8 with a single 10 mg oral dose of tofacitinib (coadministration) on Day 8 and in Cohort B, 200 mg of cyclosporine was orally administered twice daily on Days 1 to 6 with a single 10 mg oral dose of tofacitinib (coadministration) on Day 6. The adjusted geometric mean ratios of pharmacokinetic parameters of tofacitinib for comparison of tofacitinib given with tacrolimus vs. tofacitinib given alone [90% CI] were as follows: the C_{max} ratio was 90.76 [83.17, 99.03]%, the AUC_{inf} ratio was 121.12 [113.24, 129.55]%, and the $t_{1/2}$ was 3.39 ± 0.29 hours following administration of tofacitinib alone and 3.77 ± 0.49 hours following coadministration with tacrolimus. The adjusted geometric mean ratios of pharmacokinetic parameters of tofacitinib for comparison of tofacitinib given with cyclosporine vs. tofacitinib given alone were as follows: the C_{max} ratio was 83.19 [71.37, 96.96]%, the AUC_{inf} ratio was 173.13 [161.79, 185.26]%, and the $t_{1/2}$ increased from 3.21 ± 0.32 to 3.91 ± 0.32 hours following coadministration with cyclosporine.

4.(ii).A.(4).4) Ketoconazole (5.3.3.4.3, Study A3921054 [September 2010])

A study in foreign healthy adult subjects (n = 12) was conducted to estimate the effect of ketoconazole on the pharmacokinetics of tofacitinib. A single 10 mg oral dose of tofacitinib (alone) was administered and from the following day, 400 mg of ketoconazole, a CYP3A4 inhibitor, was orally administered once daily on Days 1 to 3 with a single 10 mg oral dose of tofacitinib (coadministration) on Day 3. The adjusted geometric mean ratios of pharmacokinetic parameters of tofacitinib for comparison of tofacitinib given with ketoconazole vs. tofacitinib given alone [90% CI] were as follows: the C_{max} ratio was 116.24 [104.59, 129.18]%, the AUC_{inf} ratio was 203.23 [190.96, 216.30]%, and the $t_{1/2}$ increased from 2.85 ± 0.37 to 3.91 ± 0.53 hours following coadministration with ketoconazole.

4.(ii).A.(4).5) Rifampicin (5.3.3.4.4, Study A3921056 [August to October 2010])

A study in foreign healthy adult subjects (n = 12) was conducted to estimate the effect of rifampicin on the pharmacokinetics of tofacitinib. A single 30 mg oral dose of tofacitinib (alone) was administered and from the following day, 600 mg of rifampicin, a CYP3A4 inducer, was orally administered once daily on Days 1 to 7 with a single 30 mg oral dose of tofacitinib (coadministration) on Day 8. The adjusted geometric mean ratios of pharmacokinetic parameters of tofacitinib for comparison of tofacitinib given with rifampicin vs. tofacitinib given alone [90% CI] were as follows: the C_{max} ratio was 26.32 [22.63, 30.61]%, the AUC_{inf} ratio was 16.10 [14.24, 18.20]%, and the $t_{1/2}$ decreased from 4.19 ± 0.68 to 2.86 ± 1.58 hours following coadministration with rifampicin.

4.(ii).A.(4).6) Midazolam (5.3.3.4.5, Study A3921059 [June to July 2009])

A 2-way crossover study in foreign healthy adult subjects (n = 24) was conducted to assess the effect of tofacitinib on the pharmacokinetics of midazolam, a CYP3A4 substrate. In Treatment Sequence 1, a single 2 mg oral dose of midazolam was administered (alone, Period 1) and from the following day of Period 1, 30 mg of tofacitinib was orally administered twice daily on Days 1 to 7 with a single 2 mg oral dose of midazolam on Day 7 (coadministration, Period 2). In Treatment Sequence 2, 30 mg of tofacitinib was orally administered twice daily on Days 1 to 7 with a single 2 mg oral dose of midazolam on Day 7 (coadministration, Period 1) and after a minimum of 7 days of washout, a single 2 mg oral dose of midazolam was administered (alone, Period 2). The adjusted geometric mean ratios of pharmacokinetic parameters of midazolam for comparison of midazolam given with tofacitinib vs. midazolam given alone [90% CI] were as follows: the C_{max} ratio was 102.22 [95.98, 108.87]%, the AUC_{inf} ratio was 103.97 [95.57, 113.12]%, and the $t_{1/2}$ was 4.29 ± 1.70 hours following administration of midazolam alone and 4.21 ± 1.42 hours following coadministration with tofacitinib.

4.(ii).A.(4).7) Oral contraceptives (5.3.3.4.6, Study A3921071 [June to July 2010])

A 2-way crossover study in foreign healthy adult female subjects (n = 20) was conducted to assess the effect of tofacitinib on the pharmacokinetics of oral contraceptive, a CYP3A4 substrate (a combination oral contraceptive containing 30 µg of ethinyl estradiol and 150 µg of levonorgestrel). In Treatment Sequence 1, a single dose of one tablet of oral contraceptive was administered (alone, Period 1) and from the following day of Period 1, 30 mg of tofacitinib was orally administered twice daily on Days 1 to 11 with a single dose of one tablet of oral contraceptive on Day 10 (coadministration, Period 2). In Treatment Sequence 2, 30 mg of tofacitinib was orally administered twice daily on Days 1 to 11 with a single dose of one tablet of oral contraceptive on Day 10 (coadministration, Period 1) and after at least 10 days of washout, a single dose of one tablet of oral contraceptive was administered (alone, Period 2). The adjusted geometric mean ratios of pharmacokinetic parameters for comparison of oral contraceptive given with tofacitinib vs. oral contraceptive given alone [90% CI] were as follows: the C_{max} and AUC_{inf} ratios of ethinyl estradiol were 89.62 [81.98, 97.97]% and 106.55 [98.91, 114.78]%, respectively, and the $t_{1/2}$ of ethinyl estradiol was 13.3 ± 2.24 hours following administration of oral contraceptive alone and 13.8 ± 2.30 hours following coadministration with tofacitinib and the C_{max} and AUC_{inf} ratios of levonorgestrel were 112.19 [105.30, 119.53]% and 100.87 [94.73, 107.42]%, respectively, and the $t_{1/2}$ of levonorgestrel was 25.4 ± 4.12 hours following administration of oral contraceptive alone and 25.9 ± 3.85 hours following coadministration with tofacitinib.

Based on the results from the above drug-drug interaction studies, the applicant recommended keeping the maximum dose to 5 mg BID in cases of coadministration with strong CYP3A4 inhibitors such as ketoconazole or moderate CYP3A4 and strong CYP2C19 inhibitors such as fluconazole and explained that it is necessary to caution that coadministration with CYP3A4 inducers such as rifampicin may result in loss of or reduced clinical response to tofacitinib.

4.(ii).A.(5) Pharmacodynamic studies

Healthy adult subject studies

4.(ii).A.(5).1) Effect on QTc interval (5.3.4.1.1, Study A3921028 [October 2007 to February 2008])

A placebo-controlled, randomized, double-blind,[19] 3-treatment, 3-period, crossover study in foreign healthy adult subjects (n = 60) was conducted to evaluate the effect of tofacitinib on QTc interval. A single oral dose of 100 mg of tofacitinib, 400 mg of moxifloxacin, or placebo was administered. The largest adjusted mean difference in QTcF interval between tofacitinib and placebo [two-sided 90% CI] was 2.15 [0.29, 4.00] ms (16 hours post-dose) and the upper bound of the two-sided 90% confidence interval was below 10 ms at all postdose time points and the estimated adjusted mean difference was below 5 ms. Thus, no QTc prolongation effect of tofacitinib was detected. On the other hand, the largest adjusted mean difference in QTcF interval between moxifloxacin and placebo [two-sided 90% CI] was 12.51 [10.66, 14.36] ms (4 hours post-dose). The pharmacokinetic parameters of tofacitinib were as follows: the C_{max} was 594 ± 199 ng/mL and the AUC_{inf} was 2793 ± 778 ng·hr/mL.

4.(ii).A.(5).2) Effect on glomerular filtration rate (5.3.4.1.2, Study A3921033 [October 2006 to January 2007])

A placebo-controlled, randomized, double-blind comparative study in foreign healthy adult subjects (23 subjects in the tofacitinib group, 11 subjects in the placebo group) was conducted to assess the impact of tofacitinib on renal function. Summary of the results of renal function tests (the ratios relative to Day 1) following 14-day oral administration of 15 mg of tofacitinib twice daily was as shown in Table 9 and tofacitinib had no effect on renal function tests. The pharmacokinetic parameters of tofacitinib on Day 14 (22 of 23 subjects) were as follows: the C_{max} was 108.79 ± 35.98 ng/mL and the $AUC_{0\text{-}12}$ was 393.8 ± 92.3 ng·hr/mL. Plasma concentrations were lower compared with those in other clinical studies.

Table 9. Summary of results of renal function tests following multiple oral dose administration of 15 mg of tofacitinib in foreign healthy adult subjects (Ratios relative to Day 1)

Renal function test	Day 8/Day 1 ratio		Day 15/Day 1 ratio	
	Tofacitinib 15 mg (n = 23)	Placebo (n = 11)	Tofacitinib 15 mg (n = 23)	Placebo (n = 11)
Iohexol serum clearance	1.0187 [0.9644, 1.0761]	0.9489 [0.8809, 1.0222]	0.9953 [0.9422, 1.0514]	0.9114 [0.8460, 0.9818]
Creatinine clearance	0.9389 [0.8841, 0.9970]	0.9852 [0.9324, 1.0409]	0.9477 [0.8925, 1.0064]	0.9046 [0.8561, 0.9557]
PAH clearance	-	-	0.9251 [0.8192, 1.0446]	0.9462 [0.7791, 1.1491]
Serum creatinine	1.0225 [1.0012, 1.0444]	1.0195 [0.9907, 1.0492]	0.9996 [0.9787, 1.0209]	1.0171 [0.9883, 1.0467]
eGFR[a]	0.9779 [0.9575, 0.9988]	0.9809 [0.9531, 1.0094]	1.0004 [0.9795, 1.0218]	0.9832 [0.9554, 1.0118]

Ratios of adjusted geometric means [90% CI] a) Estimated using the Cockcroft-Gault formula

RA patient studies

4.(ii).A.(5).3) Effects of tofacitinib on lymphocytes (T cell counts, B cell counts, NK cell counts) (5.3.5.3.8, PMAR-00187)

The effects of tofacitinib on the numbers of CD3+ cells (pan T-lymphocytes), CD4+ cells (helper T cells), CD8+ cells (cytotoxic T cells), CD19+ cells (B cells), and CD16/CD56+ cells (NK cells) were assessed in phase II studies in foreign RA patients (A3921019, A3921025, A3921035). Changes in CD3+, CD4+, and CD8+ counts did not show a consistent pattern of dose response. In contrast, NK cell counts (CD16/CD56+) showed dose-dependent decreases, and B-cell counts (CD19+) showed dose-dependent increases.

[19] The administration of moxifloxacin was open-label.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Racial differences in pharmacokinetics

The applicant explained the effect of race on the pharmacokinetics of tofacitinib as follows:

Concerning the pharmacokinetics of tofacitinib, tofacitinib is well-absorbed; its systemic exposure increases in proportion to the dose; tofacitinib has moderate plasma protein binding; and multiple hepatic and renal pathways are involved in the clearance. Thus, it is considered that tofacitinib is ethnically insensitive. A pharmacokinetic study in Japanese and foreign healthy adult subjects (A3921036) showed that the pharmacokinetic profile following a single oral dose of tofacitinib was similar between Japanese and foreign healthy adult subjects. Based on a population pharmacokinetic analysis of 5 Japanese and foreign phase II studies (PMAR-00178), the steady-state pharmacokinetic parameters following multiple oral doses of tofacitinib in Japanese and foreign RA patients were estimated. As a result, the $C_{max,ss}$ values at doses of 5 mg and 10 mg (geometric mean) were 60.4 to 64.2 ng/mL and 120 to 123 ng/mL, respectively, in Japanese RA patients, and 54.1 to 61.9 ng/mL and 107 to 125 ng/mL, respectively, in foreign RA patients, the $C_{min,ss}$ values (geometric mean) were 3.69 to 4.39 ng/mL and 9.07 to 9.67 ng/mL, respectively, in Japanese RA patients, and 3.38 to 4.81 ng/mL and 7.94 to 8.97 ng/mL, respectively, in foreign RA patients, and the AUC_{τ} values (geometric mean) were 262 ng·h/mL and 529 to 546 ng·h/mL, respectively, in Japanese RA patients, and 226 to 274 ng·h/mL and 470 to 541 ng·h/mL, respectively, in foreign RA patients. As the multiple-dose pharmacokinetic parameters were also estimated to be similar between Japanese and foreign RA patients, the pharmacokinetics of tofacitinib are considered similar between Japanese and foreign patients.

PMDA accepted the above explanation and considered as follows:

This clinical data package intended for registration contains foreign clinical data, based on the ICH E5 guideline etc. From a pharmacokinetic standpoint, there are no particular concerns about extrapolation of foreign clinical data.

4.(ii).B.(2) Drug-drug interactions

Drug-drug interactions between tofacitinib and CYP3A4 inhibitors or inducers may occur and it has been suggested that coadministration with strong CYP3A4 inhibitors or inducers may affect the safety and efficacy of tofacitinib. Thus, PMDA considers that the information on drugs that can cause clinically significant drug interactions with tofacitinib and the recommended dose of tofacitinib in cases of coadministration with these drugs should be adequately provided to clinical practice [see "4.(iii) Summary of clinical efficacy and safety" for the dose of tofacitinib in cases of coadministration with strong CYP3A4 inhibitors].

In addition, PMDA asked the applicant to explain the possibility that drug interactions with other drugs that are likely to be used in the treatment of RA may affect the safety and efficacy of tofacitinib.

The applicant explained as follows:

In Japanese and foreign phase III studies, commonly used RA medications other than MTX (used as concomitant or prior treatment by ≥10% of subjects) were leflunomide, methylprednisolone, prednisolone, celecoxib, and diclofenac. Thus, the safety and efficacy of tofacitinib when coadministered with these drugs were investigated.

Regarding safety, based on the data from 5 Japanese and foreign phase III studies (A3921032, A3921044, A3921045, A3921046, A3921064; 0-3 months), the incidences of adverse events by concomitant medication in the tofacitinib 5 mg and 10 mg groups were 45.1% to 54.1% and 46.4% to 57.7%, respectively, the incidences of severe adverse events by concomitant medication were 3.1% to 5.8% and 2.0% to 4.8%, respectively, and the incidences of serious adverse events by concomitant medication were 3.2% to 4.3% and 2.0% to 4.6%, respectively. The overall incidences of adverse events in the phase III studies were 51.3% and 53.8%, respectively, the overall incidences of severe adverse events were 4.0% and 3.2%, respectively, and the overall incidences of serious adverse events were 3.0% and 2.9%, respectively. Regardless of the concomitant medication used, there were no major differences from the overall incidences. In addition, no individual events occurred with a particularly high incidence following coadministration with any of these drugs.

Regarding efficacy, based on the data from 4 Japanese and foreign phase II studies (A3921025, A3921035, A3921039, A3921040) and 5 Japanese and foreign phase III studies (A3921032, A3921044, A3921045, A3921046, A3921064), the ACR20 response rates at Month 3 by concomitant medication in the tofacitinib 5 mg and 10 mg groups were 47.5% to 58.9% and 58.8% to 70.2%, respectively, and regardless of which concomitant medication was used, there were no major differences from the response rate when tofacitinib 5 mg or 10 mg was administered alone (61.4% and 69.1%, respectively).

Based on the above, drug-drug interactions between tofacitinib and these RA medications that would affect the safety and efficacy of tofacitinib are unlikely to occur.

PMDA considers as follows:
Although the clinical data suggested no particular concerns on coadministration with the above drugs, as the concomitant medications used in clinical studies were limited, it is necessary to continue to investigate the safety and efficacy of tofacitinib when coadministered with other drugs via post-marketing surveillance.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

As the safety and pharmacokinetic data etc., the results from a phase I study in Japanese and foreign healthy adult subjects (A3921036 [5.3.3.1.3]) were submitted. As the data from clinical studies in Japanese RA patients, the results from a phase II, dose response study with background MTX therapy (A3921039 [5.3.5.1.7]), a phase II, monotherapy efficacy and safety study as a bridging study (A3921040 [5.3.5.1.9]), a global phase III, MTX background, efficacy and safety study in RA patients (including Japanese patients) (A3921044 [5.3.5.1.2]), and a phase III long-term extension study in Japanese RA patients (A3921041 [5.3.5.2.1]) were submitted. As the data from clinical studies in foreign RA patients, the results from a phase II study, which served as the basis for selection of doses etc. for the global phase III study (A3921025 [5.3.5.1.6]), a phase II study as a study to be bridged (A3921035 [5.3.5.1.8]) etc., monotherapy, DMARD background, or MTX background, phase III studies (A3921045 [5.3.5.1.5], A3921046 [5.3.5.1.3], A3921064 [5.3.5.1.4], A3921032 [5.3.5.1.1]), and a phase II study of the effects of tofacitinib and atorvastatin on lipids (A3921109 [5.3.4.2.1]) etc. were

submitted [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies" for pharmacokinetic data].

4.(iii).A.(1) Healthy adult subject study

4.(iii).A.(1).1) Phase I study in Japanese and foreign healthy adult subjects (5.3.3.1.3, Study A3921036 [May to July 2007])

A placebo-controlled, randomized, dose escalation study in Japanese and foreign healthy adult subjects (Target number of cases of 24 [16 Japanese subjects, 8 foreign subjects]) was conducted to investigate the pharmacokinetics, safety, and tolerability of a single or multiple oral doses of tofacitinib.

In Cohort A, single oral doses of tofacitinib (1, 5, and 30 mg on Days 1, 4, and 7, respectively) or matching placebo were to be administered. In Cohort B, a single oral dose of 15 mg of tofacitinib or placebo and multiple oral doses of 15 mg of tofacitinib or placebo, BID for 5 days (morning and evening; morning only on Day 5) were to be administered.

All of 25 treated subjects (Cohort A, 8 Japanese subjects and 9 foreign subjects; Cohort B, 8 Japanese subjects) were included in the safety analysis set. One subject in the tofacitinib 1 mg period in Cohort A (failure to meet the inclusion criteria) and 1 subject in the placebo period in Cohort B (study drug-related adverse event) were withdrawn from the study.

In Cohort A, adverse events were reported by 1 of 6 Japanese subjects in the tofacitinib 5 mg period (constipation/musculoskeletal pain/pain in extremity/dry skin), 1 of 6 Japanese subjects in the tofacitinib 30 mg period (constipation/pain in extremity), and 1 of 2 Japanese subjects in the placebo period (pharyngolaryngeal pain) and 1 of 7 foreign subjects in the tofacitinib 1 mg period (abdominal distension/fatigue/malaise/headache), 2 of 6 foreign subjects in the tofacitinib 5 mg period (abdominal distension/asthenia/fatigue/malaise/headache [1 subject], erythema [1 subject]), 1 of 6 foreign subjects in the tofacitinib 30 mg period (abdominal distension/fatigue/headache), and 1 of 2 foreign subjects in the placebo period (aphthous stomatitis/musculoskeletal pain/headache/somnolence/cough). In Cohort B, adverse events were reported by 6 of 6 subjects in the tofacitinib period (hunger, hunger/musculoskeletal pain, skin irritation, constipation, vision blurred/dizziness/headache, and contusion [1 subject each]) and 2 of 2 subjects in the placebo period (constipation/skin irritation, diarrhoea/periodontitis).

No deaths or serious adverse events were reported. An adverse event leading to discontinuation occurred in 1 subject in the placebo period in Cohort B (periodontitis) and its causal relationship to study drug could not be denied.

In Cohort A, adverse drug reactions were reported by 1 of 6 Japanese subjects in the tofacitinib 5 mg period, 1 of 6 Japanese subjects in the tofacitinib 30 mg period, and 1 of 2 Japanese subjects in the placebo period and 1 of 7 foreign subjects in the tofacitinib 1 mg period, 1 of 6 foreign subjects in the tofacitinib 5 mg period, 1 of 6 foreign subjects in the tofacitinib 30 mg period, and 1 of 2 foreign subjects in the placebo period. In Cohort

B, adverse drug reactions were reported by 4 of 6 subjects in the tofacitinib period and 2 of 2 subjects in the placebo period.

4.(iii).A.(2) Japanese patient studies

4.(iii).A.(2).1) Phase II study in Japanese RA patients who had an inadequate response to MTX (5.3.5.1.7, Study A3921039 [January to September 2008])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in Japanese RA patients who had an inadequate response to MTX[20] (Target number of cases of 125 [25 cases per group]) was conducted to assess the dose-response relationship of tofacitinib in combination with MTX.

Subjects were to receive 1, 3, 5, or 10 mg of tofacitinib BID orally or placebo, added to background MTX. The duration of treatment was 12 weeks. Subjects were to continue to receive ≥6 mg/week of MTX supplemented with folic acid.

Of 140 randomized subjects, all 136 treated subjects (28 subjects in the tofacitinib 1 mg group, 27 subjects in the tofacitinib 3 mg group, 27 subjects in the tofacitinib 5 mg group, 26 subjects in the tofacitinib 10 mg group, 28 subjects in the placebo group) were included in the FAS (Full Analysis Set) and the safety analysis set, and included in the efficacy analyses. Withdrawals occurred in 7.1% of the tofacitinib 1 mg group (2 of 28 subjects), 14.8% of the tofacitinib 3 mg group (4 of 27 subjects), 14.8% of the tofacitinib 5 mg group (4 of 27 subjects), 19.2% of the tofacitinib 10 mg group (5 of 26 subjects), and 17.9% of the placebo group (5 of 28 subjects) and the main reasons for withdrawals were adverse events (tofacitinib 3 mg group, 7.4% [2 of 27 subjects]; tofacitinib 5 mg group, 14.8% [4 of 27 subjects]; tofacitinib 10 mg group, 15.4% [4 of 26 subjects]; placebo group, 7.1% [2 of 28 subjects]) etc.

The primary efficacy endpoint of ACR20 response rate at Week 12 was 14.3% (4 of 28 subjects) in the placebo group, 64.3% (18 of 28 subjects) in the tofacitinib 1 mg group, 77.8% (21 of 27 subjects) in the tofacitinib 3 mg group, 96.3% (26 of 27 subjects) in the tofacitinib 5 mg group, and 80.8% (21 of 26 subjects) in the tofacitinib 10 mg group and as shown in Table 10, there was a dose-response relationship for tofacitinib and statistically significant differences between the tofacitinib and placebo groups were observed. The secondary endpoints of ACR50 and ACR70 response rates at Week 12 were as shown in Table 10.

[20] Key inclusion criteria: patients who had a diagnosis of RA based upon the American College of Rheumatology criteria and active disease, fulfilling the following criteria: (a) patients had been taking MTX continuously for ≥4 months and on a stable dosage of ≥6 mg/week for ≥6 weeks prior to the first dose of study drug, (b) ≥6 swollen joints and ≥6 painful joints, and (c) CRP >7 mg/L or erythrocyte sedimentation rate (ESR) > the upper limit of normal in the local laboratory.

Table 10. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Week 12 (FAS, LOCF)

	Placebo + MTX	Tofacitinib + MTX				*P*-value[a)]
		Tofacitinib 1 mg	Tofacitinib 3 mg	Tofacitinib 5 mg	Tofacitinib 10 mg	
ACR20	14.3 (4/28)	64.3 (18/28)	77.8 (21/27)	96.3 (26/27)	80.8 (21/26)	$P < 0.0001$
ACR50	14.3 (4/28)	32.1 (9/28)	44.4 (12/27)	81.5 (22/27)	57.7 (15/26)	-
ACR70	3.6 (1/28)	7.1 (2/28)	14.8 (4/27)	33.3 (9/27)	34.6 (9/26)	-

% (n)

a) Cochran-Armitage test (a one-sided level of significance of 5%)

Adverse events occurred in 53.6% of the tofacitinib 1 mg group (15 of 28 subjects), 59.3% of the tofacitinib 3 mg group (16 of 27 subjects), 70.4% of the tofacitinib 5 mg group (19 of 27 subjects), 76.9% of the tofacitinib 10 mg group (20 of 26 subjects), and 39.3% of the placebo group (11 of 28 subjects) and the main events were as shown in Table 11.

Table 11. Adverse events reported by at least 5% of subjects in any group (Safety analysis set)

Event	Placebo (n = 28)	Tofacitinib 1 mg (n = 28)	Tofacitinib 3 mg (n = 27)	Tofacitinib 5 mg (n = 27)	Tofacitinib 10 mg (n = 26)
ALT increased	1 (3.6)	1 (3.6)	2 (7.4)	6 (22.2)	2 (7.7)
Nasopharyngitis	4 (14.3)	3 (10.7)	1 (3.7)	1 (3.7)	4 (15.4)
AST increased	1 (3.6)	1 (3.6)	2 (7.4)	4 (14.8)	1 (3.8)
Blood cholesterol increased	0	0	3 (11.1)	1 (3.7)	1 (3.8)
Low density lipoprotein increased	0	0	2 (7.4)	1 (3.7)	2 (7.7)
Blood triglycerides increased	0	1 (3.6)	1 (3.7)	1 (3.7)	2 (7.7)
Headache	1 (3.6)	2 (7.1)	0	2 (7.4)	0
Stomach discomfort	0	0	0	3 (11.1)	0
Stomatitis	0	2 (7.1)	0	0	1 (3.8)
Gastroenteritis	1 (3.6)	0	2 (7.4)	0	1 (3.8)
White blood cell count decreased	0	0	0	2 (7.4)	1 (3.8)
Pharyngitis	0	0	0	0	2 (7.7)
Rash	0	0	0	0	2 (7.7)
Erythema	2 (7.1)	1 (3.6)	0	0	0

n (%)

No deaths were reported. Serious adverse events occurred in 1 subject in the tofacitinib 1 mg group (foot deformity), 1 subject in the tofacitinib 3 mg group (osteoarthritis), 1 subject in the tofacitinib 5 mg group (femur fracture), and 2 subjects in the tofacitinib 10 mg group (cardiac failure [1 subject], dyspnoea [1 subject]) and a causal relationship to study drug could not be denied for the 1 case of cardiac failure and the 1 case of dyspnoea in the tofacitinib 10 mg group. Adverse events leading to discontinuation were observed in 2 subjects in the tofacitinib 3 mg group, 4 subjects in the tofacitinib 5 mg group, 4 subjects in the tofacitinib 10 mg group, and 2 subjects in the placebo group.

Adverse drug reactions occurred in 42.9% of the tofacitinib 1 mg group (12 of 28 subjects), 40.7% of the tofacitinib 3 mg group (11 of 27 subjects), 63.0% of the tofacitinib 5 mg group (17 of 27 subjects), 73.1% of the tofacitinib 10 mg group (19 of 26 subjects), and 28.6% of the placebo group (8 of 28 subjects).

4.(iii).A.(2).2) Phase II study in Japanese RA patients who had an inadequate response to DMARD (5.3.5.1.9, Study A3921040 [March 2009 to July 2010]) (a bridging study)

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in Japanese RA patients who had an inadequate response to DMARD[21] (Target number of cases of 300 [50 cases per group]) was conducted to assess the dose-response relationship of tofacitinib monotherapy.

Subjects were to receive 1, 3, 5, 10, or 15 mg of tofacitinib BID orally or placebo for 12 weeks.

Of 318 randomized subjects, all 317 treated subjects (53 subjects in the tofacitinib 1 mg group, 53 subjects in the tofacitinib 3 mg group, 52 subjects in the tofacitinib 5 mg group, 53 subjects in the tofacitinib 10 mg group, 54 subjects in the tofacitinib 15 mg group, 52 subjects in the placebo group) were included in the FAS (Full Analysis Set) and the safety analysis set, and included in the efficacy analyses. Withdrawals occurred in 3.8% of the tofacitinib 1 mg group (2 of 53 subjects), 7.5% of the tofacitinib 3 mg group (4 of 53 subjects), 3.8% of the tofacitinib 5 mg group (2 of 52 subjects), 7.5% of the tofacitinib 10 mg group (4 of 53 subjects), 3.7% of the tofacitinib 15 mg group (2 of 54 subjects), and 7.7% of the placebo group (4 of 52 subjects) and the main reasons for withdrawals were adverse events (tofacitinib 3 mg group, 1.9% [1 of 53 subjects]; tofacitinib 5 mg group, 3.8% [2 of 52 subjects]; tofacitinib 10 mg group, 5.7% [3 of 53 subjects]; placebo group, 3.8% [2 of 52 subjects]) etc.

The primary efficacy endpoint of ACR20 response rate at Week 12 was 15.38% (8 of 52 subjects) in the placebo group, 37.74% (20 of 53 subjects) in the tofacitinib 1 mg group, 67.92% (36 of 53 subjects) in the tofacitinib 3 mg group, 73.08% (38 of 52 subjects) in the tofacitinib 5 mg group, 84.91% (45 of 53 subjects) in the tofacitinib 10 mg group, and 90.74% (49 of 54 subjects) in the tofacitinib 15 mg group and as shown in Table 12, there was a dose-response relationship for tofacitinib and pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo. The secondary endpoints of ACR50 and ACR70 response rates at Week 12 were as shown in Table 12.

Table 12. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Week 12 (FAS, LOCF)

	Placebo	Tofacitinib 1 mg	Tofacitinib 3 mg	Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 15 mg
ACR20 response rate	15.38 (8/52)	37.74 (20/53)	67.92 (36/53)	73.08 (38/52)	84.91 (45/53)	90.74 (49/54)
Difference from placebo [95%CI][a)] *P*-value[b)]	-	22.35 [6.03, 38.68] $P = 0.0096$	52.54 [36.60, 68.48] $P < 0.0001$	57.69 [42.15, 73.23] $P < 0.0001$	69.52 [55.77, 83.27] $P < 0.0001$	75.36 [62.87, 87.84] $P < 0.0001$
ACR50 response rate	7.69 (4/52)	13.21 (7/53)	26.42 (14/53)	46.15 (24/52)	69.81 (37/53)	72.22 (39/54)
Difference from placebo [95% CI][a)]	-	5.52 [-6.13, 17.16]	18.72 [4.82, 32.63]	38.46 [23.10, 53.83]	62.12 [47.79, 76.44]	64.53 [50.56, 78.50]
ACR70 response rate	1.92 (1/52)	7.55 (4/53)	13.21 (7/53)	26.92 (14/52)	49.06 (26/53)	51.85 (28/54)
Difference from placebo [95% CI][a)]	-	5.62 [-2.41, 13.66]	11.28 [1.43, 21.13]	25.00 [12.38, 37.62]	47.13 [33.17, 61.10]	49.93 [36.09, 63.77]

% (n)

a) Normal approximation was used.

b) χ^2 test. A step-down procedure starting with the comparison of the 15 mg dose with placebo (a closed testing procedure with a fixed sequence of tests) for multiplicity adjustment.

Adverse events occurred in 39.6% of the tofacitinib 1 mg group (21 of 53 subjects), 43.4% of the tofacitinib 3 mg group (23 of 53 subjects), 55.8% of the tofacitinib 5 mg group (29 of 52 subjects), 60.4% of the tofacitinib

[21] Key inclusion criteria: patients who had a diagnosis of RA based upon the American College of Rheumatology criteria and active disease, fulfilling the following criteria: (a) patients had an inadequate response to at least one DMARD (including MTX) given continuously for ≥8 weeks or had their DMARD changed for safety reasons, (b) ≥6 tender/painful joints and ≥6 swollen joints, and (c) CRP >7 mg/L or erythrocyte sedimentation rate (ESR) > the upper limit of normal in the local laboratory.

10 mg group (32 of 53 subjects), 51.9% of the tofacitinib 15 mg group (28 of 54 subjects), and 44.2% of the placebo group (23 of 52 subjects) and the main events were as shown in Table 13.

Table 13. Adverse events reported by at least 3 subjects in any group (Safety analysis set)

Event	Placebo (n = 52)	Tofacitinib 1 mg (n = 53)	Tofacitinib 3 mg (n = 53)	Tofacitinib 5 mg (n = 52)	Tofacitinib 10 mg (n = 53)	Tofacitinib 15 mg (n = 54)
Nasopharyngitis	6 (11.5)	6 (11.3)	4 (7.5)	6 (11.5)	3 (5.7)	8 (14.8)
Hyperlipidaemia	0	1 (1.9)	0	2 (3.8)	6 (11.3)	3 (5.6)
Low density lipoprotein increased	0	0	1 (1.9)	0	1 (1.9)	6 (11.1)
Headache	1 (1.9)	1 (1.9)	3 (5.7)	2 (3.8)	1 (1.9)	0
Pharyngitis	1 (1.9)	0	0	0	3 (5.7)	2 (3.7)
Hypercholesterolaemia	0	0	2 (3.8)	0	3 (5.7)	0
Constipation	2 (3.8)	1 (1.9)	0	1 (1.9)	0	3 (5.6)
Herpes zoster	0	0	0	1 (1.9)	3 (5.7)	1 (1.9)
Fall	0	3 (5.7)	0	1 (1.9)	1 (1.9)	0
Upper respiratory tract infection	0	0	0	1 (1.9)	3 (5.7)	0
Hypertension	0	0	0	3 (5.8)	1 (1.9)	0
ALT increased	3 (5.8)	0	2 (3.8)	0	1 (1.9)	1 (1.9)
AST increased	3 (5.8)	0	1 (1.9)	0	1 (1.9)	0

n (%)

No deaths were reported. Serious adverse events occurred in 5.7% of the tofacitinib 3 mg group (3 of 53 subjects) (laboratory abnormalities,[22] gastric ulcer perforation, and rheumatoid vasculitis [1 subject each]), 3.8% of the tofacitinib 5 mg group (2 of 52 subjects) (fibula fracture/tibia fracture [1 subject], herpes zoster/post herpetic neuralgia [1 subject]), 3.8% of the tofacitinib 10 mg group (2 of 53 subjects) (tendon rupture [1 subject], herpes zoster [1 subject]), 1.9% of the tofacitinib 15 mg group (1 of 54 subjects) (herpes zoster oticus/spinal compression fracture), and 1.9% of the placebo group (1 of 52 subjects) (atelectasis). Adverse events leading to discontinuation were observed in 1 subject in the tofacitinib 3 mg group, 2 subjects in the tofacitinib 5 mg group, 3 subjects in the tofacitinib 10 mg group, and 2 subjects in the placebo group.

Adverse drug reactions were observed in 34.0% of the tofacitinib 1 mg group (18 of 53 subjects), 35.8% of the tofacitinib 3 mg group (19 of 53 subjects), 46.2% of the tofacitinib 5 mg group (24 of 52 subjects), 52.8% of the tofacitinib 10 mg group (28 of 53 subjects), 46.3% of the tofacitinib 15 mg group (25 of 54 subjects), and 38.5% of the placebo group (20 of 52 subjects).

4.(iii).A.(2).3) Global phase III study in RA patients who had an inadequate response to MTX (5.3.5.1.2, Study A3921044 [started in March 2009, ongoing (Data cut-off date of April 1, 2011, Data up to Month 12)])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in Japanese and foreign RA patients who had an inadequate response to MTX[23] (Target number of cases of 750 [300 subjects each for the tofacitinib 5 mg and 10 mg groups, 75 subjects each for the placebo→tofacitinib 5 mg and placebo→tofacitinib 10 mg groups]) was conducted in a total of 15 countries (Asia including Japan, the US, Canada, Latin America, Australia, Europe) to evaluate the efficacy and safety of tofacitinib in combination with MTX.

[22] Blood creatine phosphokinase increased, AST increased, ALT increased.

[23] Key inclusion criteria: patients who had a diagnosis of RA based upon the American College of Rheumatology criteria and active disease, fulfilling the following criteria: (a) patients had been taking MTX continuously for ≥4 months and on a stable dosage for ≥6 weeks prior to the first dose of study drug, (b) ≥3 joint erosions, or rheumatoid factor or anti-CCP positive, (c) ≥6 tender/painful joints and ≥6 swollen joints, and (d) CRP >7 mg/L or erythrocyte sedimentation rate (ESR) >28 mm/hr.

Subjects were to receive 5 mg or 10 mg of tofacitinib BID orally or placebo, added to background MTX. The duration of treatment was 2 years. Subjects were to continue to receive a stable dosage of MTX.

The study consisted of two periods (up to Month 6, the double-blind placebo-controlled period; after Month 6, the double-blind active extension period). At Month 3, subjects randomized to placebo who were determined to be non-responders[24] were advanced in a double-blind fashion to treatment with either tofacitinib 5 mg or 10 mg and at Month 6, all placebo subjects were advanced in a double-blind fashion to treatment with either tofacitinib 5 mg or 10 mg (the placebo→tofacitinib 5 mg group and the placebo→tofacitinib 10 mg group). In both the placebo and tofacitinib groups, if subjects were determined to be non-responders at Month 3, their subsequent efficacy data were treated as missing values and imputed.

The study had 4 primary efficacy endpoints: (1) ACR20 response rate at Month 6, (2) the van der Heijde modified Total Sharp Score (mTSS) change from baseline at Month 6, (3) the Health Assessment Questionnaire-Disability Index (HAQ-DI) change from baseline at Month 3, and (4) the rate of DAS28-4 (ESR) <2.6 at Month 6. A sequential gatekeeping or step-down testing procedure was planned to adjust for multiplicity from a total of 8 pairwise comparisons for 4 primary endpoints and two dose levels of tofacitinib and placebo. All pairwise comparisons were performed at a two-sided significance level of 5%. A pairwise comparison of tofacitinib 10 mg and placebo for a given endpoint could be performed only if tofacitinib 10 mg at the prior endpoint was statistically significant. A pairwise comparison of tofacitinib 5 mg and placebo for a given endpoint could be performed only if both tofacitinib 10 mg at the same endpoint, and tofacitinib 5 mg at the prior endpoint were statistically significant. For efficacy analyses of tofacitinib vs. placebo (up to Month 6), the placebo→tofacitinib 5 mg group and the placebo→tofacitinib 10 mg group were pooled and treated as a placebo group.

Of 800 randomized subjects, all 797 treated subjects (321 subjects in the tofacitinib 5 mg group, 316 subjects in the tofacitinib 10 mg group, 81 subjects in the placebo→tofacitinib 5 mg group, 79 subjects in the placebo→tofacitinib 10 mg group) were included in the safety analysis set. Of whom, 781 subjects excluding those from 2 study sites where GCP violations were identified (316 subjects in the tofacitinib 5 mg group, 309 subjects in the tofacitinib 10 mg group, 79 subjects in the placebo→tofacitinib 5 mg group, 77 subjects in the placebo→tofacitinib 10 mg group) were included in the FAS, which was used for efficacy analyses. Withdrawals during 12 months of treatment occurred in 22.1% of the tofacitinib 5 mg group (71 of 321 subjects), 16.1% of the tofacitinib 10 mg group (51 of 316 subjects), 21.0% of the placebo→tofacitinib 5 mg group (17 of 81 subjects), and 19.0% of the placebo→tofacitinib 10 mg group (15 of 79 subjects) and the main reasons for withdrawals were adverse events (tofacitinib 5 mg group, 11.2% [36 of 321 subjects]; tofacitinib 10 mg group, 8.2% [26 of 316 subjects]; placebo→tofacitinib 5 mg group, 6.2% [5 of 81 subjects]; placebo→tofacitinib 10 mg group, 7.6% [6 of 79 subjects]) etc. The proportions of subjects who were determined to be non-responders and advanced from placebo to tofacitinib at Month 3 were 51.9% (42 of 81 subjects) in the placebo→tofacitinib 5 mg group and 46.8% (37 of 79 subjects) in the placebo→tofacitinib 10

[24] Patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender/painful joint counts over baseline

mg group. The proportions of subjects who were determined to be non-responders at Month 3 were 26.2% (84 of 321 subjects) in the tofacitinib 5 mg group and 17.7% (56 of 316 subjects) in the tofacitinib 10 mg group.

Of the 797 treated subjects, 118 subjects (47 subjects in the tofacitinib 5 mg group, 47 subjects in the tofacitinib 10 mg group, 12 subjects in the placebo→tofacitinib 5 mg group, 12 subjects in the placebo→tofacitinib 10 mg group) were Japanese. In the Japanese subpopulation, withdrawals during 12 months of treatment occurred in 17.0% of the tofacitinib 5 mg group (8 of 47 subjects), 21.3% of the tofacitinib 10 mg group (10 of 47 subjects), 16.7% of the placebo→tofacitinib 5 mg group (2 of 12 subjects), and 25.0% of the placebo→tofacitinib 10 mg group (3 of 12 subjects) and the main reasons for withdrawals were adverse events (tofacitinib 5 mg group, 10.6% [5 of 47 subjects]; tofacitinib 10 mg group, 17.0% [8 of 47 subjects]; placebo→tofacitinib 10 mg group, 8.3% [1 of 12 subjects]) etc. The proportions of subjects who were determined to be non-responders and advanced from placebo to tofacitinib at Month 3 were 66.7% (8 of 12 subjects) in the placebo→tofacitinib 5 mg group and 41.7% (5 of 12 subjects) in the placebo→tofacitinib 10 mg group. The proportions of subjects who were determined to be non-responders at Month 3 were 23.4% (11 of 47 subjects) in the tofacitinib 5 mg group and 12.8% (6 of 47 subjects) in the tofacitinib 10 mg group.

The primary endpoint (1) of ACR20 response rate at Month 6 was 25.32% (39 of 154 subjects) in the placebo group, 51.46% (159 of 309 subjects) in the tofacitinib 5 mg group, and 61.81% (191 of 309 subjects) in the tofacitinib 10 mg group and as shown in Table 14, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo. The secondary endpoints of ACR50 and ACR70 response rates at Month 6 were as shown in Table 14 and the results in the Japanese subpopulation were as shown in Table 15.

Table 14. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Month 6 (FAS, NRI[a])

	Placebo (+MTX)	Tofacitinib + MTX		Difference from placebo [95% CI],[b] *P*-value[b]	
		Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 5 mg	Tofacitinib 10 mg
ACR20 response rate	25.32 (39/154)	51.46 (159/309)	61.81 (191/309)	26.13 [17.28, 34.97] *P* < 0.0001	36.48 [27.73, 45.23] *P* < 0.0001
ACR50 response rate	8.44 (13/154)	32.36 (100/309)	43.69 (135/309)	23.92 [17.10, 30.73]	35.24 [28.18, 42.30]
ACR70 response rate	1.30 (2/154)	14.56 (45/309)	22.33 (69/309)	13.26 [8.94, 17.58]	21.03 [16.05, 26.00]

% (n)
a) Non-responder imputation (NRI) method: Patients with missing values at Month 6 (patients advanced to tofacitinib and non-responders at Month 3, patients withdrawn prior to Month 6) were treated as failures.
b) Normal approximation was used.

Table 15. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Month 6 (Japanese subpopulation, NRI[a])

	Placebo (+MTX)	Tofacitinib + MTX		Difference from placebo [95% CI][b]	
		Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 5 mg	Tofacitinib 10 mg
ACR20 response rate	20.83 (5/24)	59.57 (28/47)	65.96 (31/47)	38.74 [17.27, 60.20]	45.12 [23.96, 66.27]
ACR50 response rate	8.33 (2/24)	46.81 (22/47)	55.32 (26/47)	38.47 [20.42, 56.52]	46.98 [28.97, 64.99]
ACR70 response rate	0.00 (0/24)	23.40 (11/47)	36.17 (17/47)	23.40 [11.29, 35.50]	36.17 [22.43, 49.90]

% (n)
a) Non-responder imputation (NRI) method: Patients with missing values at Month 6 (patients advanced to tofacitinib and non-responders at Month 3, patients withdrawn prior to Month 6) were treated as failures.
b) Normal approximation was used.

The primary endpoint (2) of the change from baseline in mTSS at Month 6 (mean ± SD) was 0.5 ± 2.02 in the placebo group, 0.1 ± 1.72 in the tofacitinib 5 mg group, and 0.1 ± 1.95 in the tofacitinib 10 mg group and as shown in Table 16, pairwise comparison showed a statistically significant difference between tofacitinib 10

mg and placebo and pairwise comparison showed no statistically significant difference between tofacitinib 5 mg and placebo. The results in the Japanese subpopulation were as shown in Table 16.

Table 16. Change from baseline in mTSS at Month 6 (FAS, LEP[a)])

	FAS			Japanese subpopulation		
	Placebo (+MTX)	Tofacitinib 5 mg (+MTX)	Tofacitinib 10 mg (+MTX)	Placebo (+MTX)	Tofacitinib 5 mg (+MTX)	Tofacitinib 10 mg (+MTX)
Baseline	32.6 ± 41.80 (139)	31.1 ± 47.71 (286)	37.3 ± 54.10 (295)	38.2 ± 50.07 (22)	33.9 ± 38.13 (44)	44.8 ± 62.45 (44)
Month 6	33.1 ± 42.04 (139)	31.5 ± 48.05 (277)	37.0 ± 52.78 (290)	39.7 ± 50.44 (22)	33.8 ± 37.81 (44)	45.3 ± 62.44 (44)
Change	0.5 ± 2.02 (139)	0.1 ± 1.72 (277)	0.1 ± 1.95 (290)	1.4 ± 3.15 (22)	-0.0 ± 1.09 (44)	0.5 ± 1.54 (44)
Difference from placebo [95% CI][b)]	-	-0.34 [-0.73, 0.04]	-0.40 [-0.79, -0.02]	-	-1.49 [-2.45, -0.54]	-0.94 [-1.90, 0.01]
P-value[b)]	-	0.0792	0.0376	-	-	-

Mean ±SD (n)

a) Missing values at Month 6 (patients advanced to tofacitinib and non-responders at Month 3, patients withdrawn prior to Month 6) were imputed using a linear extrapolation method.

b) ANCOVA model with treatment, site, and baseline value as explanatory variables.

The primary endpoint (3) of the change from baseline in HAQ-DI at Month 3 (mean ± SD) was −0.1 ± 0.48 in the placebo group, −0.4 ± 0.58 in the tofacitinib 5 mg group, and −0.6 ± 0.53 in the tofacitinib 10 mg group and as shown in Table 17, pairwise comparison showed a statistically significant difference between tofacitinib 10 mg and placebo. The results in the Japanese subpopulation were as shown in Table 17.

Table 17. HAQ-DI over time and changes from baseline (FAS[a)])

	FAS			Japanese subpopulation		
	Placebo (+MTX)	Tofacitinib 5 mg (+MTX)	Tofacitinib 10 mg (+MTX)	Placebo (+MTX)	Tofacitinib 5 mg (+MTX)	Tofacitinib 10 mg (+MTX)
Baseline	1.31 ± 0.68 (156)	1.41 ± 0.68 (315)	1.39 ± 0.66 (309)	1.10 ± 0.75 (24)	1.23 ± 0.65 (47)	1.35 ± 0.53 (47)
Month 1	1.25 ± 0.67 (153) -0.1 ± 0.38	1.16 ± 0.67 (309) -0.3 ± 0.45	1.02 ± 0.65 (308) -0.4 ± 0.48	1.06 ± 0.65 (24) -0.0 ± 0.36	0.98 ± 0.58 (47) -0.3 ± 0.36	0.95 ± 0.57 (47) -0.4 ± 0.45
Month 3	1.19 ± 0.69 (146) -0.1 ± 0.48	1.00 ± 0.65 (295) -0.4 ± 0.58	0.84 ± 0.65 (300) -0.6 ± 0.53	1.11 ± 0.73 (21) -0.0 ± 0.48	0.70 ± 0.55 (44) -0.5 ± 0.49	0.69 ± 0.57 (44) -0.7 ± 0.49
Difference from placebo at Month 3 [95% CI][b)]	-	-0.25 [-0.34, -0.16]	-0.40 [-0.49, -0.31]	-	-0.46 [-0.67, -0.24]	-0.57 [-0.79, -0.35]
P-value[b)]	-	-[c)]	$P < 0.0001$	-	-	-

Mean ± SD (n) Lower row: HAQ-DI change from baseline

a) No imputation was applied to missing data.

b) Using 6-month data, a linear mixed-effect model with repeated measures including treatment, visit, treatment-by-visit interaction, baseline value, and site as fixed effects and subject as a random effect, assuming a compound symmetry covariance structure

c) As treatment difference in the primary endpoint (2) between tofacitinib 5 mg and placebo was not statistically significant, a pairwise comparison of tofacitinib 5 mg and placebo was not performed.

The primary endpoint (4) of the rate of DAS28-4 (ESR) <2.6 at Month 6 was 1.55% (2 of 129 subjects) in the placebo group, 7.17% (19 of 265 subjects) in the tofacitinib 5 mg group, and 15.95% (41 of 257 subjects) in the tofacitinib 10 mg group and as shown in Table 18, pairwise comparison showed a statistically significant difference between tofacitinib 10 mg and placebo. The results in the Japanese subpopulation were as shown in Table 18.

Table 18. Rate of DAS28-4 (ESR) <2.6 at Month 6 (FAS, NRI[a])

	Placebo (+MTX)	Tofacitinib + MTX		Difference from placebo [95% CI][b] *P*-value[b]	
		Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 5 mg	Tofacitinib 10 mg
FAS	1.55 (2/129)	7.17 (19/265)	15.95 (41/257)	5.61 [1.85, 9.38] -[c]	14.40 [9.44, 19.36] *P* < 0.0001
Japanese subpopulation	6.25 (1/16)	14.71 (5/34)	31.25 (10/32)	8.45 [-8.34, 25.26]	25.00 [5.03, 44.96]

% (n)

a) Non-responder imputation (NRI) method: Patients with missing values (patients advanced to tofacitinib and non-responders at Month 3, patients withdrawn prior to Month 6) were treated as failures.

b) Normal approximation was used.

c) As treatment difference in the primary endpoint (2) between tofacitinib 5 mg and placebo was not statistically significant, a pairwise comparison of tofacitinib 5 mg and placebo was not performed.

In the safety analysis set, adverse events in Months 0 to 3 occurred in 48.9% of the tofacitinib 5 mg group (157 of 321 subjects), 54.1% of the tofacitinib 10 mg group (171 of 316 subjects), and 45.6% of the placebo group (73 of 160 subjects) and the main events were as shown in Table 19.

Adverse events in Months 3 to 6 occurred in 45.2% of the tofacitinib 5 mg group (145 of 321 subjects), 35.1% of the tofacitinib 10 mg group (111 of 316 subjects), 25.9% of the placebo group (21 of 81 subjects), 42.9% of the placebo→tofacitinib 5 mg group (18 of 42 subjects), and 40.5% of the placebo→tofacitinib 10 mg group (15 of 37 subjects) and the main events were nasopharyngitis (tofacitinib 5 mg group, 3.7% [12 of 321 subjects]; tofacitinib 10 mg group, 2.2% [7 of 316 subjects]; placebo group, 4.9% [4 of 81 subjects]; placebo→tofacitinib 5 mg group, 2.4% [1 of 42 subjects]; placebo→tofacitinib 10 mg group, 5.4% [2 of 37 subjects]) and upper respiratory tract infection (tofacitinib 5 mg group, 4.7% [15 of 321 subjects]; tofacitinib 10 mg group, 1.9% [6 of 316 subjects]; placebo→tofacitinib 5 mg group, 4.8% [2 of 42 subjects]; placebo→tofacitinib 10 mg group, 8.1% [3 of 37 subjects]) etc.

Adverse events in Months 6 to 12 occurred in 51.7% of the tofacitinib 5 mg group (166 of 321 subjects), 55.1% of the tofacitinib 10 mg group (174 of 316 subjects), 42.0% of the placebo→tofacitinib 5 mg group (34 of 81 subjects), and 44.3% of the placebo→tofacitinib 10 mg group (35 of 79 subjects) and the main events were nasopharyngitis (tofacitinib 5 mg group, 6.2% [20 of 321 subjects]; tofacitinib 10 mg group, 6.0% [19 of 316 subjects]; placebo→tofacitinib 5 mg group, 2.5% [2 of 81 subjects]; placebo→tofacitinib 10 mg group, 3.8% [3 of 79 subjects]) and upper respiratory tract infection (tofacitinib 5 mg group, 3.1% [10 of 321 subjects]; tofacitinib 10 mg group, 3.8% [12 of 316 subjects]; placebo→tofacitinib 5 mg group, 3.7% [3 of 81 subjects]; placebo→tofacitinib 10 mg group, 3.8% [3 of 79 subjects]) etc.

Table 19. Adverse events reported by at least 2% of subjects in any group (0-3 months, Safety analysis set)

Event	Placebo (n = 160)	Tofacitinib 5 mg (n = 321)	Tofacitinib 10 mg (n = 316)
Nasopharyngitis	1 (0.6)	14 (4.4)	13 (4.1)
Headache	3 (1.9)	18 (5.6)	4 (1.3)
Upper respiratory tract infection	5 (3.1)	9 (2.8)	7 (2.2)
Hypertension	1 (0.6)	11 (3.4)	4 (1.3)
Diarrhoea	2 (1.3)	7 (2.2)	8 (2.5)
Urinary tract infection	4 (2.5)	9 (2.8)	3 (0.9)
Cough	1 (0.6)	1 (0.3)	9 (2.8)
Nausea	2 (1.3)	7 (2.2)	3 (0.9)
Arthralgia	5 (3.1)	5 (1.6)	3 (0.9)
Rheumatoid arthritis	4 (2.5)	1 (0.3)	0

n (%)

In the safety analysis set, four deaths occurred in the tofacitinib 5 mg group (basal cell carcinoma/pneumonia, acute respiratory distress syndrome/viral pneumonia, metastatic lung cancer, and pyrexia/pneumocystis jiroveci pneumonia/disseminated intravascular coagulation/multi-organ failure [1 subject each]), one in the tofacitinib 10 mg group (spinal column stenosis/aspiration), and one in the placebo→tofacitinib 5 mg group (cardiac arrest/acute renal failure/bacterial sepsis/hydronephrosis/pyelonephritis/diabetic nephropathy) and their causal relationship to study drug could not be denied except for disseminated intravascular coagulation/multi-organ failure in the tofacitinib 5 mg group and spinal column stenosis/aspiration in the tofacitinib 10 mg group. Serious adverse events occurred in 12.1% of the tofacitinib 5 mg group (39 of 321 subjects), 7.3% of the tofacitinib 10 mg group (23 of 316 subjects), 6.2% of the placebo→tofacitinib 5 mg group (5 of 81 subjects), and 13.9% of the placebo→tofacitinib 10 mg group (11 of 79 subjects) and the main events were as shown in Table 20. Adverse events leading to discontinuation were reported by 12.1% of the tofacitinib 5 mg group (39 of 321 subjects), 9.2% of the tofacitinib 10 mg group (29 of 316 subjects), 9.9% of the placebo group (8 of 81 subjects), 3.7% of the placebo→tofacitinib 5 mg group (3 of 81 subjects), and 5.1% of the placebo→tofacitinib 10 mg group (4 of 79 subjects).

Table 20. Serious adverse events reported by at least 2 subjects in the study (Safety analysis set)

Event	Tofacitinib 5 mg (n = 321)	Tofacitinib 10 mg (n = 316)	Placebo→Tofacitinib 5 mg (n = 81)	Placebo→Tofacitinib 10 mg (n = 79)
Pneumonia	5	1	0	0
Sciatica	1	1	0	0
Chest pain	0	1	0	1
Herpes zoster	2	0	0	0
Rheumatoid arthritis	1	0	0	1
Cellulitis	2	0	0	0
Skin ulcer	2	0	0	0
Intervertebral disc protrusion	1	0	0	1
Basal cell carcinoma	1	0	0	1
Cholelithiasis	2	0	0	0
Road traffic accident	0	1	0	1

n

Adverse drug reactions in Months 0 to 3 occurred in 30.5% of the tofacitinib 5 mg group (98 of 321 subjects), 33.2% of the tofacitinib 10 mg group (105 of 316 subjects), and 25.6% of the placebo group (41 of 160 subjects), adverse drug reactions in Months 3 to 6 occurred in 27.4% of the tofacitinib 5 mg group (88 of 321 subjects), 19.3% of the tofacitinib 10 mg group (61 of 316 subjects), 12.3% of the placebo group (10 of 81 subjects), 33.3% of the placebo→tofacitinib 5 mg group (14 of 42 subjects), and 29.7% of the placebo→tofacitinib 10 mg group (11 of 37 subjects), and adverse drug reactions in Months 6 to 12 occurred in 31.2% of the tofacitinib 5 mg group (100 of 321 subjects), 32.0% of the tofacitinib 10 mg group (101 of 316 subjects), 27.2% of the placebo→tofacitinib 5 mg group (22 of 81 subjects), and 31.6% of the placebo→tofacitinib 10 mg group (25 of 79 subjects).

In the Japanese subpopulation, adverse events in Months 0 to 3 occurred in 53.2% of the tofacitinib 5 mg group (25 of 47 subjects), 68.1% of the tofacitinib 10 mg group (32 of 47 subjects), and 37.5% of the placebo group (9 of 24 subjects) and the main events were as shown in Table 21.

Adverse events in Months 3 to 6 occurred in 57.4% of the tofacitinib 5 mg group (27 of 47 subjects), 42.6% of the tofacitinib 10 mg group (20 of 47 subjects), 36.4% of the placebo group (4 of 11 subjects), 50.0% of the placebo→tofacitinib 5 mg group (4 of 8 subjects), and 60.0% of the placebo→tofacitinib 10 mg group (3 of 5

subjects) and the main events were nasopharyngitis (tofacitinib 5 mg group, 12.8% [6 of 47 subjects]; tofacitinib 10 mg group, 6.4% [3 of 47 subjects]; placebo group, 18.2% [2 of 11 subjects]; placebo→tofacitinib 10 mg group, 20.0% [1 of 5 subjects]) and ALT increased (tofacitinib 5 mg group, 8.5% [4 of 47 subjects]; tofacitinib 10 mg group, 6.4% [3 of 47 subjects]; placebo→tofacitinib 5 mg group, 12.5% [1 of 8 subjects]) etc.

Adverse events in Months 6 to 12 occurred in 68.1% of the tofacitinib 5 mg group (32 of 47 subjects), 68.1% of the tofacitinib 10 mg group (32 of 47 subjects), 66.7% of the placebo→tofacitinib 5 mg group (8 of 12 subjects), and 50.0% of the placebo→tofacitinib 10 mg group (6 of 12 subjects) and the main events were nasopharyngitis (tofacitinib 5 mg group, 23.4% [11 of 47 subjects]; tofacitinib 10 mg group, 23.4% [11 of 47 subjects]; placebo→tofacitinib 5 mg group, 16.7% [2 of 12 subjects]; placebo→tofacitinib 10 mg group, 16.7% [2 of 12 subjects]) and herpes zoster (tofacitinib 5 mg group, 2.1% [1 of 47 subjects]; tofacitinib 10 mg group, 6.4% [3 of 47 subjects]; placebo→tofacitinib 5 mg group, 16.7% [2 of 12 subjects]; placebo→tofacitinib 10 mg group, 16.7% [2 of 12 subjects]) etc.

Table 21. Adverse events reported by at least 2 subjects in any group (0-3 months, Japanese subpopulation)

Event	Placebo (n = 24)	Tofacitinib 5 mg (n = 47)	Tofacitinib 10 mg (n = 47)
Nasopharyngitis	1 (4.2)	5 (10.6)	7 (14.9)
ALT increased	0	0	4 (8.5)
Pyrexia	0	3 (6.4)	1 (2.1)
Herpes zoster	0	1 (2.1)	3 (6.4)
Pharyngitis	0	1 (2.1)	2 (4.3)
Stomatitis	1 (4.2)	2 (4.3)	1 (2.1)
Diarrhoea	0	2 (4.3)	1 (2.1)
Gastroenteritis	0	1 (2.1)	2 (4.3)
Blood cholesterol increased	0	1 (2.1)	2 (4.3)
White blood cell count decreased	0	1 (2.1)	2 (4.3)
Constipation	0	2 (4.3)	0
Vomiting	0	2 (4.3)	0
Influenza	0	0	2 (4.3)
AST increased	0	0	2 (4.3)
Weight increased	0	0	2 (4.3)
Rash	0	0	2 (4.3)

n (%)

In the Japanese subpopulation, two deaths occurred in the tofacitinib 5 mg group (metastatic lung cancer, pyrexia/pneumocystis jiroveci pneumonia/disseminated intravascular coagulation/multi-organ failure) and their causal relationship to study drug could not be denied. Serious adverse events occurred in 12.8% of the tofacitinib 5 mg group (6 of 47 subjects) (skin ulcer [2 subjects], gastric cancer/metastases to lymph nodes, pyrexia/pneumocystis jiroveci pneumonia/disseminated intravascular coagulation/multi-organ failure, metastatic lung cancer, and herpes zoster [1 subject each]), 14.9% of the tofacitinib 10 mg group (7 of 47 subjects) (bacterial enterocolitis, radius fracture, enteritis, influenza, spinal compression fracture, cytomegalovirus viraemia, and lymphoma [1 subject each]), and 8.3% of the placebo→tofacitinib 10 mg group (1 of 12 subjects) (basal cell carcinoma). Adverse events leading to discontinuation were reported by 10.6% of the tofacitinib 5 mg group (5 of 47 subjects) and 19.1% of the tofacitinib 10 mg group (9 of 47 subjects).

In the Japanese subpopulation, adverse drug reactions in Months 0 to 3 occurred in 48.9% of the tofacitinib 5 mg group (23 of 47 subjects), 59.6% of the tofacitinib 10 mg group (28 of 47 subjects), and 29.2% of the placebo group (7 of 24 subjects), adverse drug reactions in Months 3 to 6 occurred in 51.1% of the tofacitinib

5 mg group (24 of 47 subjects), 38.3% of the tofacitinib 10 mg group (18 of 47 subjects), 36.4% of the placebo group (4 of 11 subjects), 50.0% of the placebo→tofacitinib 5 mg group (4 of 8 subjects), and 60.0% of the placebo→tofacitinib 10 mg group (3 of 5 subjects), and adverse drug reactions in Months 6 to 12 occurred in 61.7% of the tofacitinib 5 mg group (29 of 47 subjects), 57.4% of the tofacitinib 10 mg group (27 of 47 subjects), 58.3% of the placebo→tofacitinib 5 mg group (7 of 12 subjects), and 50.0% of the placebo→tofacitinib 10 mg group (6 of 12 subjects).

4.(iii).A.(2).4) Phase III long-term extension study in Japanese RA patients (5.3.5.2.1, Study A3921041 [started in April 2008, ongoing [Data cut-off date of September 16, 2011])

An open-label, uncontrolled study in Japanese RA patients who completed Japanese phase II studies (Study A3921039 and Study A3921040) and a global phase III study (Study A3921044) (Target number of cases of 400) was conducted to assess the long-term safety of tofacitinib as a monotherapy or in combination with DMARD including MTX.

Subjects were to initiate at a dose of tofacitinib 5 mg BID orally. The dosage may be increased from 5 mg BID to 10 mg BID, reduced from 10 mg BID to 5 mg BID, or temporarily discontinued (up to 28 consecutive days) based on the investigator's consideration of the risks and benefits to the patient.[25] Study treatment was initiated within 7 days of the final visit of the previous study and continued until up to 6 months after marketing approval in Japan.

All of 427 treated subjects (113 subjects rolled-over from Study A3921039, 291 subjects rolled-over from Study A3921040, 23 subjects rolled-over from Study A3921044) were included in the FAS and the safety analysis set, and included in the efficacy analyses. Withdrawals occurred in 18.3% of subjects (78 of 427 subjects) and the main reasons for withdrawals were adverse events (15.2% [65 of 427 subjects]). The median treatment duration (range) in this study was 546.0 days (5-1231 days).[26] The tofacitinib 10 mg group was defined as subjects treated with tofacitinib 10 mg BID for a total of ≥84 days and 81 of 427 subjects were classified as the tofacitinib 10 mg group.

The efficacy endpoints of ACR20, ACR50, and ACR70 response rates were as shown in Table 22.

Table 22. ACR20, ACR50, and ACR70 response rates over time

	Week 12	Week 36	Week 72	Week 144
ACR20 response rate	87.3 (345/395)	92.2 (341/370)	91.1 (257/282)	92.4 (73/79)
ACR50 response rate	63.0 (249/395)	71.6 (265/370)	76.2 (215/282)	75.9 (60/79)
ACR70 response rate	38.7 (153/395)	46.5 (172/370)	53.9 (152/282)	55.7 (44/79)

% (n)

The incidence of adverse events was 93.2% (398 of 427 subjects) and the main events were as shown in Table 23.

[25] Although the initial version of the protocol stated that the dosage may be reduced from 5 mg BID to 1 to 4 mg BID, the protocol was amended as stated above (Protocol Amendment 2, the 3rd version of the protocol as of March 9, 2009).

[26] The duration of treatment with tofacitinib was 1070.0 days (approximately 2.9 years; range, 5-1231 days) in subjects rolled-over from Study A3921039, 509.0 days (approximately 1.4 years; range, 8-769 days) in subjects rolled-over from Study A3921040, and 28.0 days (approximately 1 month, 7-62 days) in subjects rolled over from Study A3921044.

Table 23. Adverse events reported by at least 3% of subjects (Safety analysis set, n = 427)

Event	Tofacitinib
Nasopharyngitis	200 (46.8)
Herpes zoster	51 (11.9)
Fall	37 (8.7)
Hyperlipidaemia	37 (8.7)
Headache	37 (8.7)
Dental caries	35 (8.2)
Hypertension	35 (8.2)
Upper respiratory tract infection	30 (7.0)
Contusion	30 (7.0)
Cystitis	29 (6.8)
Constipation	29 (6.8)
Bronchitis	25 (5.9)
Pharyngitis	25 (5.9)
Back pain	25 (5.9)
Influenza	24 (5.6)
Tinea pedis	23 (5.4)
Lymphocyte count decreased	23 (5.4)
Diarrhoea	21 (4.9)
Gastroenteritis	21 (4.9)
Gastritis	20 (4.7)
Oral herpes	20 (4.7)
Stomatitis	20 (4.7)
Cough	20 (4.7)
ALT increased	19 (4.4)
Upper respiratory tract inflammation	19 (4.4)
Pyrexia	18 (4.2)
Low density lipoprotein increased	17 (4.0)
Onychomycosis	16 (3.7)
White blood cell count decreased	16 (3.7)
AST increased	16 (3.7)
Rash	15 (3.5)
Iron deficiency anaemia	15 (3.5)
Hypercholesterolaemia	15 (3.5)
Conjunctivitis	15 (3.5)
Vertigo	14 (3.3)
Periodontitis	14 (3.3)
Abdominal discomfort	14 (3.3)
Oropharyngeal pain	13 (3.0)
Eczema	13 (3.0)

n (%)

Two deaths occurred (interstitial lung disease/rheumatoid arthritis/liver disorder/pleurisy/disseminated intravascular coagulation/thrombotic thrombocytopenic purpura [1 subject], ovarian cancer/malignant ascites/malignant pleural effusion/metastases to lymph nodes/omentum neoplasm [1 subject]) and their causal relationship to study drug could not be denied. The incidence of serious adverse events was 16.9% (72 of 427 subjects) and the main events were herpes zoster (7 subjects), tendon rupture (5 subjects), pneumonia (4 subjects), gastric cancer, pyelonephritis, and spinal column stenosis (3 subjects each), and haemophilus pneumonia, femoral neck fracture, rheumatoid arthritis, and joint dislocation (2 subjects each) etc. The incidence of adverse events leading to discontinuation was 14.8% (63 of 427 subjects) and the incidence of adverse drug reactions was 87.8% (375 of 427 subjects).

4.(iii).A.(3) Foreign patient studies

4.(iii).A.(3).1) Late phase II study in RA patients who had an inadequate response to MTX (5.3.5.1.6, Study A3921025 [January 2007 to August 2008])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in foreign RA patients who had an inadequate response to MTX[27] (Target number of cases of 483 [69 cases per group]) was conducted to evaluate the efficacy and safety of tofacitinib in combination with MTX.

Subjects were to receive tofacitinib 1, 3, 5, 10, or 15 mg BID or 20 mg QD or placebo BID orally, added to background MTX. The duration of treatment was 6 months. Subjects were to continue to receive a stable dosage of MTX supplemented with folic acid and a single dosage reduction of MTX (≤5 mg/week) was allowed for subjects with a confirmed elevation of transaminase levels. Subjects randomized to tofacitinib 1 mg BID, 3 mg BID, 20 mg QD, and placebo who were determined to be non-responders[28] at Week 12 were advanced in a double-blind fashion to tofacitinib 5 mg BID (a dose already demonstrated to be efficacious in Study A3921019[29]).

Of 509 randomized subjects, all 507 treated subjects (70 subjects in the tofacitinib 1 mg group, 68 subjects in the tofacitinib 3 mg group, 71 subjects in the tofacitinib 5 mg group, 74 subjects in the tofacitinib 10 mg group, 75 subjects in the tofacitinib 15 mg group, 80 subjects in the tofacitinib 20 mg QD group, 69 subjects in the placebo group) were included in the FAS and the safety analysis set, and included in the efficacy analyses. Withdrawals occurred in 12.9% of the tofacitinib 1 mg group (9 of 70 subjects), 16.2% of the tofacitinib 3 mg group (11 of 68 subjects), 21.1% of the tofacitinib 5 mg group (15 of 71 subjects), 10.8% of the tofacitinib 10 mg group (8 of 74 subjects), 20.0% of the tofacitinib 15 mg group (15 of 75 subjects), 17.5% of the tofacitinib 20 mg QD group (14 of 80 subjects), and 21.7% of the placebo group (15 of 69 subjects) and the main reasons for withdrawals were adverse events (tofacitinib 1 mg group, 4.3% [3 of 70 subjects]; tofacitinib 3 mg group, 4.4% [3 of 68 subjects]; tofacitinib 5 mg group, 4.2% [3 of 71 subjects]; tofacitinib 10 mg group, 6.8% [5 of 74 subjects]; tofacitinib 15 mg group, 13.3% [10 of 75 subjects]; tofacitinib 20 mg QD group, 7.5% [6 of 80 subjects]; placebo group, 4.3% [3 of 69 subjects]) etc. At Month 3, 26.1% of the placebo group (18 of 69 subjects), 30.0% of the tofacitinib 1 mg group (21 of 70 subjects), 19.1% of the tofacitinib 3 mg group (13 of 68 subjects), and 16.3% of the tofacitinib 20 mg QD group (13 of 80 subjects) were determined to be non-responders and advanced to tofacitinib 5 mg BID.

The primary efficacy endpoint of ACR20 response rate at Week 12 was 36.23% (25 of 69 subjects) in the placebo group, 47.14% (33 of 70 subjects) in the tofacitinib 1 mg group, 55.88% (38 of 68 subjects) in the tofacitinib 3 mg group, 56.34% (40 of 71 subjects) in the tofacitinib 5 mg group, 58.11% (43 of 74 subjects) in the tofacitinib 10 mg group, 56.00% (42 of 75 subjects) in the tofacitinib 15 mg group, and 56.25% (45 of

[27] Key inclusion criteria: patients who had a diagnosis of RA based upon the American College of Rheumatology criteria and active disease, fulfilling the following criteria: (a) patients had been taking MTX continuously for ≥4 months and on a stable dosage (7.5-25 mg/week) for ≥6 weeks prior to the first dose of study drug, (b) rheumatoid factor positive, (c) ≥6 tender/painful joints and ≥6 swollen joints, and (d) CRP >7 mg/L or erythrocyte sedimentation rate (ESR) > the upper limit of normal in the local laboratory.

[28] Patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender/painful joint counts over baseline

[29] A study that evaluated the efficacy and safety of tofacitinib in RA patients who had an inadequate response or intolerance to prior MTX (≥15 mg/week) or etanercept, infliximab, or adalimumab. Subjects were to receive 5, 15, or 30 mg of tofacitinib or placebo BID orally and the duration of treatment was 6 weeks. A total of 264 subjects were treated (61 subjects in the tofacitinib 5 mg group, 69 subjects in the tofacitinib 15 mg group, 69 subjects in the tofacitinib 30 mg group, 65 subjects in the placebo group).

80 subjects) in the tofacitinib 20 mg QD group and as shown in Table 24, based on an Emax model, there were statistically significant differences between the tofacitinib and placebo groups. The secondary endpoints of ACR50 and ACR70 response rates at Week 12 were as shown in Table 24.

Table 24. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Week 12 (FAS, BOCF)

	Placebo + MTX	Tofacitinib + MTX					Tofacitinib 20 mg QD + MTX	*P*-value[a)]
		Tofacitinib 1 mg	Tofacitinib 3 mg	Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 15 mg		
ACR20 response rate	36.23 (25/69)	47.14 (33/70)	55.88 (38/68)	56.34 (40/71)	58.11 (43/74)	56.00 (42/75)	56.25 (45/80)	$P = 0.0053$
ACR50 response rate	17.39 (12/69)	22.86 (16/70)	29.41 (20/68)	36.62 (26/71)	28.38 (21/74)	44.00 (33/75)	36.25 (29/80)	-
ACR70 response rate	5.80 (4/69)	4.29 (3/70)	20.59 (14/68)	18.31 (13/71)	12.16 (9/74)	24.00 (18/75)	23.75 (19/80)	-

% (n)

a) An E_{max} model was fit by using a pre-specified ED_{50} value of 5 mg BID that was chosen based upon analyses of Study A3921019 and a logistic regression model with an intercept and dose/(ED_{50}+dose) as explanatory variables was used and the test of statistical significance of whether the E_{max} parameter, i.e. the slope on dose/(ED50+dose), was 0 (a trend test), was performed. Tofacitinib 20 mg QD group was not included.

Adverse events in 0 to 12 weeks occurred in 48.6% of the tofacitinib 1 mg group (34 of 70 subjects), 58.8% of the tofacitinib 3 mg group (40 of 68 subjects), 54.9% of the tofacitinib 5 mg group (39 of 71 subjects), 64.9% of the tofacitinib 10 mg group (48 of 74 subjects), 60.0% of the tofacitinib 15 mg group (45 of 75 subjects), 55.0% of the tofacitinib 20 mg QD group (44 of 80 subjects), and 53.6% of the placebo group (37 of 69 subjects) and the main events were as shown in Table 25.

Adverse events in 0 to 24 weeks (double-blind phase) occurred in 59.2% of the tofacitinib 1 mg group (29 of 49 subjects), 66.7% of the tofacitinib 1 mg→5 mg group (14 of 21 subjects), 69.1% of the tofacitinib 3 mg group (38 of 55 subjects), 76.9% of the tofacitinib 3 mg→5 mg group (10 of 13 subjects), 66.2% of the tofacitinib 5 mg group (47 of 71 subjects), 67.6% of the tofacitinib 10 mg group (50 of 74 subjects), 76.0% of the tofacitinib 15 mg group (57 of 75 subjects), 61.2% of the tofacitinib 20 mg QD group (41 of 67 subjects), 46.2% of the tofacitinib 20 mg QD→5 mg group (6 of 13 subjects), 56.9% of the placebo group (29 of 51 subjects), and 66.7% of the placebo→tofacitinib 5 mg group (12 of 18 subjects) and the main events were diarrhoea (tofacitinib 1 mg group, 14.3% [7 of 49 subjects]; tofacitinib 1 mg→5 mg group, 4.8% [1 of 21 subjects]; tofacitinib 3 mg group, 1.8% [1 of 55 subjects]; tofacitinib 3 mg→5 mg group, 7.7% [1 of 13 subjects]; tofacitinib 5 mg group, 12.7% [9 of 71 subjects]; tofacitinib 10 mg group, 1.4% [1 of 74 subjects]; tofacitinib 15 mg group, 4.0% [3 of 75 subjects]; tofacitinib 20 mg QD group, 1.5% [1 of 67 subjects]; tofacitinib 20 mg QD→5 mg group, 7.7% [1 of 13 subjects]; placebo group, 3.9% [2 of 51 subjects]) etc.

Table 25. Adverse events reported by at least 5% of subjects in any group (0-12 weeks, Safety analysis set)

Event	Tofacitinib 1 mg (n = 70)	Tofacitinib 3 mg (n = 68)	Tofacitinib 5 mg (n = 71)	Tofacitinib 10 mg (n = 74)	Tofacitinib 15 mg (n = 75)	Tofacitinib 20 mg (n = 80)	Placebo (n = 69)
Headache	3 (4.3)	2 (2.9)	2 (2.8)	2 (2.7)	2 (2.7)	10 (12.5)	1 (1.4)
Nausea	3 (4.3)	4 (5.9)	3 (4.2)	5 (6.8)	4 (5.3)	2 (2.5)	1 (1.4)
Urinary tract infection	1 (1.4)	4 (5.9)	4 (5.6)	1 (1.4)	4 (5.3)	5 (6.3)	0
Diarrhoea	5 (7.1)	2 (2.9)	7 (9.9)	1 (1.4)	1 (1.3)	1 (1.3)	2 (2.9)
Upper respiratory tract infection	0	3 (4.4)	5 (7.0)	1 (1.4)	2 (2.7)	4 (5.0)	2 (2.9)
Nasopharyngitis	1 (1.4)	1 (1.5)	4 (5.6)	2 (2.7)	3 (4.0)	2 (2.5)	3 (4.3)
Cough	1 (1.4)	2 (2.9)	3 (4.2)	5 (6.8)	1 (1.3)	3 (3.8)	0
Influenza	1 (1.4)	1 (1.5)	1 (1.4)	4 (5.4)	3 (4.0)	1 (1.3)	0
AST increased	0	1 (1.5)	0	0	5 (6.7)	2 (2.5)	0
ALT increased	1 (1.4)	1 (1.5)	0	0	5 (6.7)	1 (1.3)	1 (1.4)

n (%)

One death occurred in the tofacitinib 3 mg group (pneumonia/respiratory failure/cardiac failure) and a causal relationship to study drug could not be denied for pneumonia. Serious adverse events were reported by 2 subjects in the tofacitinib 1 mg group (chest pain [1 subject], colon neoplasm [1 subject]), 1 subject in the tofacitinib 1 mg→5 mg group (uterine haemorrhage), 3 subjects in the tofacitinib 3 mg group (urinary tract infection, syncope, and arthralgia [1 subject each]), 4 subjects in the tofacitinib 5 mg group (pneumonia, congestive cardiac failure, blindness, and melanocytic naevus [1 subject each]), 1 subject in the tofacitinib 10 mg group (lower respiratory tract infection), 6 subjects in the tofacitinib 15 mg group (gastric ulcer, dissociative disorder, chest pain, chest discomfort, ankle fracture, and stomatitis [1 subject each]), and 4 subjects in the tofacitinib 20 mg QD group (atrial fibrillation, pneumonia, pyrexia, and food poisoning [1 subject each]). Adverse events leading to discontinuation were reported by 3 subjects in the tofacitinib 1 mg group, 2 subjects in the tofacitinib 3 mg group, 3 subjects in the tofacitinib 5 mg group, 5 subjects in the tofacitinib 10 mg group, 9 subjects in the tofacitinib 15 mg group, 6 subjects in the tofacitinib 20 mg QD group, and 3 subjects in the placebo group.

Adverse drug reactions in 0 to 12 weeks occurred in 24.3% of the tofacitinib 1 mg group (17 of 70 subjects), 29.4% of the tofacitinib 3 mg group (20 of 68 subjects), 18.3% of the tofacitinib 5 mg group (13 of 71 subjects), 39.2% of the tofacitinib 10 mg group (29 of 74 subjects), 32.0% of the tofacitinib 15 mg group (24 of 75 subjects), 30.0% of the tofacitinib 20 mg QD group (24 of 80 subjects), and 24.6% of the placebo group (17 of 69 subjects). Adverse drug reactions in 0 to 24 weeks (double-blind phase) occurred in 18.4% of the tofacitinib 1 mg group (9 of 49 subjects), 57.1% of the tofacitinib 1 mg→5 mg group (12 of 21 subjects), 36.4% of the tofacitinib 3 mg group (20 of 55 subjects), 23.1% of the tofacitinib 3 mg→5mg group (3 of 13 subjects), 25.4% of the tofacitinib 5 mg group (18 of 71 subjects), 44.6% of the tofacitinib 10 mg group (33 of 74 subjects), 38.7% of the tofacitinib 15 mg group (29 of 75 subjects), 31.3% of the tofacitinib 20 mg QD group (21 of 67 subjects), 30.8% of the tofacitinib 20 mg QD→5 mg group (4 of 13 subjects), 25.5% of the placebo group (13 of 51 subjects), and 27.8% of the placebo→tofacitinib 5 mg group (5 of 18 subjects).

4.(iii).A.(3).2) Late phase II study in RA patients who had an inadequate response to DMARD (5.3.5.1.8, Study A3921035 [September 2007 to January 2009]) (a study to be bridged)

A placebo- and adalimumab-controlled, randomized, double-blind, parallel-group, comparative study in foreign RA patients who had an inadequate response to DMARD[30] (Target number of cases of 350 [50 cases per group]) was conducted to assess the dose-response relationship of tofacitinib monotherapy.

Subjects were to receive tofacitinib 1, 3, 5, 10, or 15 mg BID orally or placebo for 6 months or adalimumab 40 mg subcutaneous injection every other week for 10 weeks followed by tofacitinib 5 mg BID for 3 months. Subjects randomized to tofacitinib 1 mg, 3 mg, and placebo who were determined to be non-responders[31] at Month 3 were advanced in a double-blind fashion to tofacitinib 5 mg BID (a dose already demonstrated to be efficacious in Study A3921019).

[30] Key inclusion criteria: patients who had a diagnosis of RA based upon the American College of Rheumatology criteria and active disease, fulfilling the following criteria: (a) patients who had failed at least 1 DMARD treatment due to lack of efficacy or toxicity, (b) ≥6 tender/painful joints and ≥6 swollen joints, and (c) CRP >7 mg/L or erythrocyte sedimentation rate (ESR) > the upper limit of normal in the local laboratory.

[31] Patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender/painful joint counts over baseline

Of 386 randomized subjects, all 384 treated subjects (54 subjects in the tofacitinib 1 mg group, 51 subjects in the tofacitinib 3 mg group, 49 subjects in the tofacitinib 5 mg group, 61 subjects in the tofacitinib 10 mg group, 57 subjects in the tofacitinib 15 mg group, 53 subjects in the adalimumab group, 59 subjects in the placebo group) were included in the FAS and the safety analysis set, and included in the efficacy analyses. Withdrawals occurred in 25.9% of the tofacitinib 1 mg group (14 of 54 subjects), 15.1% of the tofacitinib 3 mg group (8 of 51 subjects), 12.2% of the tofacitinib 5 mg group (6 of 49 subjects), 9.8% of the tofacitinib 10 mg group (6 of 61 subjects), 8.8% of the tofacitinib 15 mg group (5 of 57 subjects), 30.2% of the adalimumab group (16 of 53 subjects), and 27.1% of the placebo group (16 of 59 subjects) and the main reasons for withdrawals were lack of efficacy (tofacitinib 1 mg group, 7.4% [4 of 54 subjects]; tofacitinib 3 mg group, 3.9% [2 of 51 subjects]; tofacitinib 5 mg group, 2.0% [1 of 49 subjects]; tofacitinib 10 mg group, 1.6% [1 of 61 subjects]; adalimumab group, 9.4% [5 of 53 subjects]; placebo group, 6.8% [4 of 59 subjects]) etc. At Month 3, 42.4% of the placebo group (25 of 59 subjects), 31.5% of the tofacitinib 1 mg group (17 of 54 subjects), and 33.3% of the tofacitinib 3 mg group (17 of 51 subjects) were determined to be non-responders and advanced to tofacitinib 5 mg BID.

The primary efficacy endpoint of ACR20 response rate at Week 12 was 23.73% (14 of 59 subjects) in the placebo group, 31.48% (17 of 54 subjects) in the tofacitinib 1 mg group, 45.10% (23 of 51 subjects) in the tofacitinib 3 mg group, 61.22% (30 of 49 subjects) in the tofacitinib 5 mg group, 72.13% (44 of 61 subjects) in the tofacitinib 10 mg group, 71.93% (41 of 57 subjects) in the tofacitinib 15 mg group, and 39.62% (21 of 53 subjects) in the adalimumab group and as shown in Table 26, a dose-response trend for tofacitinib was observed and based on an Emax model, there were statistically significant differences between the tofacitinib and placebo groups. The secondary endpoints of ACR50 and ACR70 response rates at Week 12 were as shown in Table 26.

Table 26. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Week 12 (FAS, BOCF)

	Placebo	Tofacitinib 1 mg	Tofacitinib 3 mg	Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 15 mg	Adalimumab	*P*-value[a)]
ACR20 response rate	23.73 (14/59)	31.48 (17/54)	45.10 (23/51)	61.22 (30/49)	72.13 (44/61)	71.93 (41/57)	39.62 (21/53)	$P < 0.0001$
ACR50 response rate	10.17 (6/59)	11.11 (6/54)	25.49 (13/51)	38.78 (19/49)	45.90 (28/61)	50.88 (29/57)	20.75 (11/53)	-
ACR70 response rate	3.39 (2/59)	5.56 (3/54)	11.76 (6/51)	14.29 (7/49)	24.59 (15/61)	26.32 (15/57)	3.77 (2/53)	-

% (n)
a) An E_{max} model was fit by using a pre-specified ED_{50} value of 5 mg BID that was chosen based upon analyses of Study A3921019 and a logistic regression model with an intercept and dose/(ED_{50}+dose) as explanatory variables was used and the test of statistical significance of whether the E_{max} parameter, i.e. the slope on dose/(ED_{50}+dose), was 0 (a trend test), was performed. Adalimumab group was not included.

Adverse events in 0 to 12 weeks occurred in 35.2% of the tofacitinib 1 mg group (19 of 54 subjects), 37.3% of the tofacitinib 3 mg group (19 of 51 subjects), 49.0% of the tofacitinib 5 mg group (24 of 49 subjects), 50.8% of the tofacitinib 10 mg group (31 of 61 subjects), 52.6% of the tofacitinib 15 mg group (30 of 57 subjects), 50.9% of the adalimumab group (27 of 53 subjects), and 40.7% of the placebo group (24 of 59 subjects) and the main events were as shown in Table 27.

Adverse events in 0 to 24 weeks (double-blind phase) occurred in 51.4% of the tofacitinib 1 mg group (19 of 37 subjects), 29.4% of the tofacitinib 1 mg→5 mg group (5 of 17 subjects), 52.9% of the tofacitinib 3 mg group (18 of 34 subjects), 35.3% of the tofacitinib 3 mg→5 mg group (6 of 17 subjects), 55.1% of the tofacitinib 5 mg group (27 of 49 subjects), 59.0% of the tofacitinib 10 mg group (36 of 61 subjects), 61.4% of

the tofacitinib 15 mg group (35 of 57 subjects), 55.6% of the adalimumab group (5 of 9 subjects), 63.6% of the adalimumab→tofacitinib 5 mg group (28 of 44 subjects), 47.1% of the placebo group (16 of 34 subjects), and 52.0% of the placebo→tofacitinib 5 mg group (13 of 25 subjects) and the most commonly reported event was urinary tract infection (tofacitinib 1 mg group, 8.1% [3 of 37 subjects]; tofacitinib 3 mg group, 5.9% [2 of 34 subjects]; tofacitinib 3 mg→5 mg group, 5.9% [1 of 17 subjects]; tofacitinib 5 mg group, 10.2% [5 of 49 subjects]; tofacitinib 10 mg group, 4.9% [3 of 61 subjects]; tofacitinib 15 mg group, 10.5% [6 of 57 subjects]; adalimumab→tofacitinib 5 mg group, 4.5% [2 of 44 subjects]; placebo group, 5.9% [2 of 34 subjects]; placebo→tofacitinib 5 mg group, 4.0% [1 of 25 subjects]).

Table 27. Adverse events reported by at least 3 subjects in any group (0-12 weeks, Safety analysis set)

Event	Placebo (n = 59)	Tofacitinib 1 mg (n = 54)	Tofacitinib 3 mg (n = 51)	Tofacitinib 5 mg (n = 49)	Tofacitinib 10 mg (n = 61)	Tofacitinib 15 mg (n = 57)	Adalimumab (n = 53)
Urinary tract infection	3 (5.1)	2 (3.7)	1 (2.0)	5 (10.2)	2 (3.3)	4 (7.0)	2 (3.8)
Diarrhoea	1 (1.7)	2 (3.7)	2 (3.9)	2 (4.1)	4 (6.6)	1 (1.8)	1 (1.9)
Headache	1 (1.7)	0	2 (3.9)	2 (4.1)	5 (8.2)	2 (3.5)	2 (3.8)
Bronchitis	1 (1.7)	1 (2.9)	2 (3.9)	2 (4.1)	1 (1.6)	4 (7.0)	3 (5.7)
Nausea	0	2 (3.7)	1 (2.0)	1 (2.0)	3 (4.9)	2 (3.5)	2 (3.8)
Upper respiratory tract infection	2 (3.4)	2 (3.7)	0	2 (4.1)	3 (4.9)	2 (3.5)	0
Dizziness	1 (1.7)	2 (3.7)	0	0	2 (3.3)	3 (5.3)	2 (3.8)
Rash	1 (1.7)	1 (2.9)	0	1 (2.0)	0	3 (5.3)	2 (3.8)
Hypertension	1 (1.7)	0	0	1 (2.0)	3 (4.9)	1 (1.8)	0
Chest discomfort	0	0	0	0	0	3 (5.3)	0

n (%)

One death occurred in the tofacitinib 15 mg group (cerebrovascular accident), but its causal relationship to study drug was denied. Serious adverse events were reported by 2 subjects in the tofacitinib 1 mg group (pneumonia [2 subjects]), 1 subject in the tofacitinib 3 mg group (anaemia/gastric ulcer), 1 subject in the tofacitinib 10 mg group (meniscus injury/osteoarthritis), 4 subjects in the tofacitinib 15 mg group (gastritis, depressed level of consciousness, intervertebral disc protrusion, and bacterial meningitis/pneumococcal sepsis/pneumococcal pneumonia/sinusitis [1 subject each]), 4 subjects in the adalimumab group (acute pyelonephritis, knee arthroplasty, postmenopausal haemorrhage, and renal cell carcinoma [1 subject each]), and 2 subjects in the placebo group (panic attack [1 subject], wound infection [1 subject]). Adverse events leading to discontinuation were reported by 7.4% of the tofacitinib 1 mg group (4 of 54 subjects), 5.9% of the tofacitinib 3 mg group (3 of 51 subjects), 2.0% of the tofacitinib 5 mg group (1 of 49 subjects), 1.6% of the tofacitinib 10 mg group (1 of 61 subjects), 5.3% of the tofacitinib 15 mg group (3 of 57 subjects), 13.2% of the adalimumab group (7 of 53 subjects), and 1.7% of the placebo group (1 of 59 subjects).

Adverse drug reactions in 0 to 12 weeks occurred in 20.4% of the tofacitinib 1 mg group (11 of 54 subjects), 17.6% of the tofacitinib 3 mg group (9 of 51 subjects), 20.4% of the tofacitinib 5 mg group (10 of 49 subjects), 36.1% of the tofacitinib 10 mg group (22 of 61 subjects), 36.8% of the tofacitinib 15 mg group (21 of 57 subjects), 35.8% of the adalimumab group (19 of 53 subjects), and 15.3% of the placebo group (9 of 59 subjects). Adverse drug reactions in 0 to 24 weeks (double-blind phase) occurred in 27.0% of the tofacitinib 1 mg group (10 of 37 subjects), 17.6% of the tofacitinib 1 mg→5 mg group (3 of 17 subjects), 20.6% of the tofacitinib 3 mg group (7 of 34 subjects), 23.5% of the tofacitinib 3 mg→5 mg group (4 of 17 subjects), 24.5% of the tofacitinib 5 mg group (12 of 49 subjects), 39.3% of the tofacitinib 10 mg group (24 of 61 subjects), 36.8% of the tofacitinib 15 mg group (21 of 57 subjects), 33.3% of the adalimumab group (3 of 9 subjects), 38.6% of the adalimumab→tofacitinib 5 mg group (17 of 44 subjects), 20.6% of the placebo group (7 of 34 subjects), and 16.0% of the placebo→tofacitinib 5 mg group (4 of 25 subjects).

4.(iii).A.(3).3) Phase III study in RA patients who had an inadequate response to DMARD (5.3.5.1.5, Study A3921045 [February 2009 to June 2010])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in foreign RA patients who had an inadequate response to DMARD[32] (Target number of cases of 500 [200 subjects each for the tofacitinib 5 mg and 10 mg groups, 50 subjects each for the placebo→tofacitinib 5 mg and placebo→tofacitinib 10 mg groups]) was conducted to evaluate the efficacy and safety of tofacitinib monotherapy.

Subjects were to receive 5 or 10 mg of tofacitinib BID orally or placebo and the duration of treatment was 6 months. Subjects randomized to placebo (the placebo→tofacitinib 5 mg group and the placebo→tofacitinib 10 mg group) were advanced in a double-blind fashion to tofacitinib 5 or 10 mg BID at Month 3.

The study had 3 primary efficacy endpoints: (1) ACR20 response rate at Month 3, (2) the mean change from baseline in HAQ-DI at Month 3, and (3) the rate of DAS28-4 (ESR) <2.6 at Month 3. A sequential gatekeeping or step-down testing procedure was planned to adjust for multiplicity from a total of 6 pairwise comparisons for 3 primary endpoints and two dose levels of tofacitinib and placebo. All pairwise comparisons were performed at a two-sided significance level of 5%. A pairwise comparison of tofacitinib 10 mg and placebo for a given endpoint could be performed only if tofacitinib 10 mg at the prior endpoint was statistically significant. A pairwise comparison of tofacitinib 5 mg and placebo for a given endpoint could be performed only if both tofacitinib 10 mg at the same endpoint, and tofacitinib 5 mg at the prior endpoint were statistically significant. For efficacy analyses of tofacitinib vs. placebo (up to Month 3), the placebo→tofacitinib 5 mg group and the placebo→tofacitinib 10 mg group were pooled and treated as a placebo group.

Of 611 randomized subjects, all 610 treated subjects (243 subjects in the tofacitinib 5 mg group, 245 subjects in the tofacitinib 10 mg group, 61 subjects in the placebo→tofacitinib 5 mg group, 61 subjects in the placebo→tofacitinib 10 mg group) were included in the FAS and the safety analysis set, and included in the efficacy analyses. Withdrawals occurred in 4.5% of the tofacitinib 5 mg group (11 of 243 subjects), 11.0% of the tofacitinib 10 mg group (27 of 245 subjects), 11.5% of the placebo→tofacitinib 5 mg group (7 of 61 subjects), and 16.4% of the placebo→tofacitinib 10 mg group (10 of 61 subjects) and the main reasons for withdrawals were adverse events (tofacitinib 5 mg group, 1.2% [3 of 243 subjects]; tofacitinib 10 mg group, 3.7% [9 of 245 subjects]; placebo→tofacitinib 5 mg group, 4.9% [3 of 61 subjects]; placebo→tofacitinib 10 mg group, 3.3% [2 of 61 subjects]) etc.

The primary endpoint (1) of ACR20 response rate at Month 3 was 26.67% (32 of 120 subjects) in the placebo group, 59.75% (144 of 241 subjects) in the tofacitinib 5 mg group, and 65.70% (159 of 242 subjects) in the tofacitinib 10 mg group and as shown in Table 28, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo. The secondary endpoints of ACR50 and ACR70 response rates at Month 3 were as shown in Table 28.

[32] Key inclusion criteria: patients who had a diagnosis of RA based upon the American College of Rheumatology criteria and active disease, fulfilling the following criteria: (a) patients who had failed at least 1 DMARD treatment (traditional DMARDs including MTX or biologic DMARDs) due to lack of efficacy or toxicity, (b) ≥6 tender/painful joints and ≥6 swollen joints, and (c) CRP >7 mg/L or erythrocyte sedimentation rate (ESR) >28 mm/hr.

Table 28. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Month 3 (FAS, NRI[a])

	Placebo	Tofacitinib		Difference from placebo [95% CI][b] *P*-value[b]	
		Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 5 mg	Tofacitinib 10 mg
ACR20 response rate	26.67 (32/120)	59.75 (144/241)	65.70 (159/242)	33.08 [23.04, 43.13] *P* < 0.0001	39.04 [29.12, 48.95] *P* < 0.0001
ACR50 response rate	12.50 (15/120)	31.12 (75/241)	36.78 (89/242)	18.62 [10.30, 26.94]	24.28 [15.80, 32.76]
ACR70 response rate	5.83 (7/120)	15.35 (37/241)	20.25 (49/242)	9.52 [3.33, 15.71]	14.41 [7.84, 20.99]

% (n)
a) Non-responder imputation (NRI) method: Patients with missing values were treated as failures.
b) Normal approximation was used.

The primary endpoint (2) of the change from baseline in HAQ-DI at Month 3 (mean ± SD) was −0.18 ± 0.61 in the placebo group, −0.48 ± 0.66 in the tofacitinib 5 mg group, and −0.54 ± 0.60 in the tofacitinib 10 mg group and as shown in Table 29, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo.

Table 29. HAQ-DI over time and changes from baseline (FAS[a])

	Placebo	Tofacitinib 5 mg	Tofacitinib 10 mg
Baseline	1.53 ± 0.65 (122)	1.53 ± 0.66 (240)	1.50 ± 0.64 (241)
Week 2	1.43 ± 0.64 (119) -0.11 ± 0.42	1.27 ± 0.62 (240) -0.27 ± 0.49	1.21 ± 0.65 (239) -0.29 ± 0.46
Month 1	1.40 ± 0.64 (116) -0.13 ± 0.44	1.18 ± 0.68 (237) -0.35 ± 0.58	1.09 ± 0.66 (240) -0.41 ± 0.54
Month 2	1.40 ± 0.68 (110) -0.13 ± 0.55	1.05 ± 0.66 (240) -0.48 ± 0.61	0.97 ± 0.68 (233) -0.53 ± 0.61
Month 3	1.35 ± 0.73 (109) -0.18 ± 0.61	1.05 ± 0.70 (238) -0.48 ± 0.66	0.97 ± 0.69 (229) -0.54 ± 0.60
Difference from placebo at Month 3 [95% CI][b] *P*-value[b]	-	-0.31 [-0.43, -0.20] *P* < 0.0001	-0.38 [-0.50, -0.27] *P* < 0.0001

Mean ± SD (n) Lower row: HAQ-DI change from baseline
a) No imputation was applied to missing data.
b) A linear mixed-effect model with repeated measures including treatment, visit, treatment-by-visit interaction, baseline value, and site as fixed effects and subject as a random effect, assuming a compound symmetry covariance structure

The primary endpoint (3) of the rate of DAS28-4 (ESR) <2.6 at Month 3 was 4.39% (5 of 114 subjects) in the placebo group, 5.60% (13 of 232 subjects) in the tofacitinib 5 mg group, and 8.73% (20 of 229 subjects) in the tofacitinib 10 mg group and as shown in Table 30, there were no statistically significant differences between 10 or 5 mg of tofacitinib and placebo.

Table 30. Rate of DAS28-4 (ESR) <2.6 at Month 3 (FAS, NRI[a])

Placebo	Tofacitinib		Difference from placebo [95% CI][b] *P*-value[b]	
	Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 5 mg	Tofacitinib 10 mg
4.39 (5/114)	5.60 (13/232)	8.73 (20/229)	1.22 [-3.57, 6.00] -[c]	4.35 [-0.90, 9.59] *P* = 0.1042

% (n)
a) Non-responder imputation (NRI) method: Patients with missing values were treated as failures.
b) Normal approximation was used.
c) As treatment difference between tofacitinib 10 mg and placebo was not statistically significant, a pairwise comparison of tofacitinib 5 mg and placebo was not performed in order to control the type I error rate at the nominal level or below.

Adverse events in 0 to 3 months occurred in 51.0% of the tofacitinib 5 mg group (124 of 243 subjects), 56.7% of the tofacitinib 10 mg group (139 of 245 subjects), and 54.9% of the placebo group (67 of 122 subjects) and the main events were as shown in Table 31.

Adverse events in 3 to 6 months occurred in 39.9% of the tofacitinib 5 mg group (97 of 243 subjects), 41.2% of the tofacitinib 10 mg group (101 of 245 subjects), 36.1% of the placebo→tofacitinib 5 mg group (22 of 61

subjects), and 39.3% of the placebo→tofacitinib 10 mg group (24 of 61 subjects) and the main events were upper respiratory tract infection (tofacitinib 5 mg group, 4.1% [10 of 243 subjects]; tofacitinib 10 mg group, 2.9% [7 of 245 subjects]; placebo→tofacitinib 5 mg group, 6.6% [4 of 61 subjects]; placebo→tofacitinib 10 mg group, 1.6% [1 of 61 subjects]) and headache (tofacitinib 5 mg group, 3.3% [8 of 243 subjects]; tofacitinib 10 mg group, 1.6% [4 of 245 subjects]; placebo→tofacitinib 5 mg group, 1.6% [1 of 61 subjects]; placebo→tofacitinib 10 mg group, 4.9% [3 of 61 subjects]) etc.

Table 31. Adverse events reported by at least 2% of subjects in any group (0-3 months, Safety analysis set)

Event	Placebo (n = 122)	Tofacitinib 5 mg (n = 243)	Tofacitinib 10 mg (n = 245)
Headache	3 (2.5)	13 (5.3)	11 (4.5)
Diarrhoea	3 (2.5)	11 (4.5)	9 (3.7)
Upper respiratory tract infection	6 (4.9)	11 (4.5)	8 (3.3)
Nausea	3 (2.5)	7 (2.9)	9 (3.7)
Urinary tract infection	3 (2.5)	4 (1.6)	10 (4.1)
Blood creatine phosphokinase increased	1 (0.8)	3 (1.2)	10 (4.1)
Peripheral oedema	3 (2.5)	7 (2.9)	5 (2.0)
Dyspepsia	4 (3.3)	5 (2.1)	6 (2.4)
Anaemia	2 (1.6)	4 (1.6)	6 (2.4)
Upper abdominal pain	0	6 (2.5)	4 (1.6)
Constipation	3 (2.5)	5 (2.1)	5 (2.0)
Back pain	2 (1.6)	5 (2.1)	5 (2.0)
Hypertension	2 (1.6)	2 (0.8)	7 (2.9)
Gastritis	3 (2.5)	3 (1.2)	6 (2.4)
Nasopharyngitis	2 (1.6)	4 (1.6)	5 (2.0)
Rheumatoid arthritis	1 (0.8)	6 (2.5)	2 (0.8)
Dizziness	4 (3.3)	3 (1.2)	5 (2.0)
Paraesthesia	0	6 (2.5)	1 (0.4)
Influenza	4 (3.3)	2 (0.8)	4 (1.6)
Arthralgia	3 (2.5)	2 (0.8)	2 (0.8)
Pyrexia	3 (2.5)	2 (0.8)	1 (0.4)

n (%)

One death occurred in the tofacitinib 10 mg group (cardiac arrest/hyperkalaemia/asthenia/multi-organ failure/congestive cardiac failure), but its causal relationship to study drug was denied. Serious adverse events were reported by 6 subjects in the tofacitinib 5 mg group (lower limb fracture, hypoglycaemia, chronic obstructive pulmonary disease, thrombocytopenia, cellulitis, and humerus fracture/patella fracture [1 subject each]), 10 subjects in the tofacitinib 10 mg group (vertigo/vomiting/hyponatraemia/myocardial infarction, congestive cardiac failure/chronic obstructive pulmonary disease/atrial fibrillation/bronchitis, non-small cell lung cancer/pulmonary fibrosis/diabetes mellitus, tuberculous pleurisy, liver abscess, acute cholecystitis, abdominoplasty/breast prosthesis implantation, chronic obstructive pulmonary disease, chronic pyelonephritis, and asthenia/congestive cardiac failure/multi-organ failure [1 subject each]), 4 subjects in the placebo→tofacitinib 5 mg group (pulmonary embolism/deep vein thrombosis/cellulitis, grand mal convulsion, rheumatoid arthritis, and transient ischaemic attack [1 subject each]), and 2 subjects in the placebo→tofacitinib 10 mg group (sleep apnoea syndrome [1 subject], uterine leiomyoma/uterine polyp [1 subject]). Adverse events leading to discontinuation were reported by 3 subjects in the tofacitinib 5 mg group, 10 subjects in the tofacitinib 10 mg group, 3 subjects in the placebo→tofacitinib 5 mg group, and 2 subjects in the placebo→tofacitinib 5 mg group.

Adverse drug reactions in 0 to 3 months occurred in 25.9% of the tofacitinib 5 mg group (63 of 243 subjects), 31.4% of the tofacitinib 10 mg group (77 of 245 subjects), and 27.0% of the placebo group (33 of 122 subjects) and adverse drug reactions in 3 to 6 months occurred in 16.0% of the tofacitinib 5 mg group (39 of 243 subjects),

22.4% of the tofacitinib 10 mg group (55 of 245 subjects), 21.3% of the placebo→tofacitinib 5 mg group (13 of 61 subjects), and 18.0% of the placebo→tofacitinib 10 mg group (11 of 61 subjects).

4.(iii).A.(3).4) Phase III study in RA patients who had an inadequate response to DMARD (5.3.5.1.3, Study A3921046 [May 2009 to January 2011])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in foreign RA patients who had an inadequate response to DMARD[33] (Target number of cases of 750 [300 subjects each for the tofacitinib 5 mg and 10 mg groups, 75 subjects each for the placebo→tofacitinib 5 mg and placebo→tofacitinib 10 mg groups]) was conducted to evaluate the efficacy and safety of tofacitinib in combination with DMARD.

Subjects were to receive 5 or 10 mg of tofacitinib BID orally or placebo, added to background DMARD. The duration of treatment was 12 months. Subjects were to remain on at least 1 background traditional DMARD excluding potent immunosuppressive treatments such as azathioprine or cyclosporine and be dosed in accordance with the local regulatory label and remain on that traditional DMARD throughout the course of the study.[34]

The study consisted of two periods (up to Month 6, the double-blind placebo-controlled period; after Month 6, the double-blind active extension period) and subjects randomized to placebo (the placebo→tofacitinib 5 mg group and the placebo→tofacitinib 10 mg group) who were determined to be non-responders[35] at Month 3 were advanced in a double-blind fashion to tofacitinib 5 or 10 mg and all placebo subjects were advanced in a double-blind fashion to tofacitinib 5 or 10 mg at Month 6. In both the placebo and tofacitinib groups, if subjects were determined to be non-responders at Month 3, their subsequent efficacy data were treated as missing values and imputed.

The study had 3 primary efficacy endpoints: (1) ACR20 response rate at Month 6, (2) the mean change from baseline in HAQ-DI at Month 3, and (3) the rate of DAS28-4 (ESR) <2.6 at Month 6. A sequential gatekeeping or step-down testing procedure was planned to adjust for multiplicity from a total of 6 pairwise comparisons for 3 primary endpoints and two dose levels of tofacitinib and placebo. All pairwise comparisons were performed at a two-sided significance level of 5%. A pairwise comparison of tofacitinib 10 mg and placebo for a given endpoint could be performed only if tofacitinib 10 mg at the prior endpoint was statistically significant. A pairwise comparison of tofacitinib 5 mg and placebo for a given endpoint could be performed only if both tofacitinib 10 mg at the same endpoint, and tofacitinib 5 mg at the prior endpoint were statistically significant. For efficacy analyses of tofacitinib vs. placebo (up to Month 3), the placebo→tofacitinib 5 mg group and the placebo→tofacitinib 10 mg group were pooled and treated as a placebo group.

[33] Key inclusion criteria: patients who had a diagnosis of RA based upon the American College of Rheumatology criteria and active disease, fulfilling the following criteria: (a) patients who had failed at least 1 DMARD (traditional DMARDs including MTX or biologic DMARDs) due to lack of efficacy or toxicity, (b) ≥4 tender/painful joints and ≥4 swollen joints, and (c) CRP >7 mg/L or erythrocyte sedimentation rate (ESR) >28 mm/hr.

[34] Washout of all potent immunosuppressive treatments and biologic DMARDs was required. The commonly used background DMARDs were MTX and leflunomide etc.

[35] Patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender/painful joint counts over baseline

Of 795 randomized subjects, all 792 treated subjects (315 subjects in the tofacitinib 5 mg group, 318 subjects in the tofacitinib 10 mg group, 79 subjects in the placebo→tofacitinib 5 mg group, 80 subjects in the placebo→tofacitinib 10 mg group) were included in the FAS and the safety analysis set, and included in the efficacy analyses. Withdrawals occurred in 17.1% of the tofacitinib 5 mg group (54 of 315 subjects), 20.8% of the tofacitinib 10 mg group (66 of 318 subjects), 10.1% of the placebo→tofacitinib 5 mg group (8 of 79 subjects), and 16.3% of the placebo→tofacitinib 10 mg group (13 of 80 subjects) and the main reasons for withdrawals were adverse events (tofacitinib 5 mg group, 6.3% [20 of 315 subjects]; tofacitinib 10 mg group, 9.1% [29 of 318 subjects]; placebo→tofacitinib 5 mg group, 2.5% [2 of 79 subjects]; placebo→tofacitinib 10 mg group, 3.8% [3 of 80 subjects]) and lack of efficacy (tofacitinib 5 mg group, 5.1% [16 of 315 subjects]; tofacitinib 10 mg group, 3.8% [12 of 318 subjects]; placebo→tofacitinib 5 mg group, 3.8% [3 of 79 subjects]; placebo→tofacitinib 10 mg group, 3.8% [3 of 80 subjects]) etc. The proportions of subjects who were determined to be non-responders and advanced from placebo to tofacitinib at Month 3 were 48.1% (38 of 79 subjects) in the placebo→tofacitinib 5 mg group and 50% (40 of 80 subjects) in the placebo→tofacitinib 10 mg group.

The primary endpoint (1) of ACR20 response rate at Month 6 was 31.21% (49 of 157 subjects) in the placebo group, 52.73% (164 of 311 subjects) in the tofacitinib 5 mg group, and 58.25% (180 of 309 subjects) in the tofacitinib 10 mg group and as shown in Table 32, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo. The secondary endpoints of ACR50 and ACR70 response rates at Month 6 were as shown in Table 32.

Table 32. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Month 6 (FAS, NRI[a])

	Placebo + DMARD	Tofacitinib + DMARD		Difference from placebo [95% CI][b] *P*-value[b]	
		Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 5 mg	Tofacitinib 10 mg
ACR20 response rate	31.21 (49/157)	52.73 (164/311)	58.25 (180/309)	21.52 [12.39, 30.65] *P* < 0.0001	27.04 [17.94, 36.13] *P* < 0.0001
ACR50 response rate	12.74 (20/157)	33.76 (105/311)	36.57 (113/309)	21.02 [13.61, 28.42]	23.83 [16.34, 31.31]
ACR70 response rate	3.18 (5/157)	13.18 (41/311)	16.18 (50/309)	9.99 [5.34, 14.65]	12.99 [8.05, 17.93]

% (n)
a) Non-responder imputation (NRI) method: Patients with missing values (patients advanced to tofacitinib and non-responders at Month 3, patients withdrawn prior to Month 6) were treated as failures.
b) Normal approximation was used.

The primary endpoint (2) of the change from baseline in HAQ-DI at Month 3 (mean ± SD) was −0.16 ± 0.54 in the placebo group, −0.45 ± 0.53 in the tofacitinib 5 mg group, and −0.54 ± 0.60 in the tofacitinib 10 mg group and as shown in Table 33, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo.

Table 33. HAQ-DI over time and changes from baseline (FAS[a])

	Placebo + DMARD	Tofacitinib 5 mg + DMARD	Tofacitinib 10 mg + DMARD
Baseline	1.35 ± 0.66 (157)	1.44 ± 0.69 (311)	1.43 ± 0.68 (315)
Week 2	1.28 ± 0.66 (156) -0.06 ± 0.35	1.24 ± 0.69 (310) -0.20 ± 0.42	1.14 ± 0.67 (305) -0.28 ± 0.45
Month 1	1.20 ± 0.67 (154) -0.14 ± 0.40	1.12 ± 0.67 (304) -0.31 ± 0.50	1.01 ± 0.65 (303) -0.41 ± 0.55
Month 2	1.20 ± 0.63 (150) -0.14 ± 0.49	1.03 ± 0.68 (299) -0.41 ± 0.51	0.93 ± 0.66 (300) -0.49 ± 0.56
Month 3	1.16 ± 0.67 (148) -0.16 ± 0.54	0.98 ± 0.67 (293) -0.45 ± 0.53	0.88 ± 0.67 (292) -0.54 ± 0.60
Difference from placebo at Month 3 [95% CI][b] *P*-value[b]	-	-0.26 [-0.35, -0.16] *P* < 0.0001	-0.35 [-0.44, -0.26] *P* < 0.0001

Mean ± SD (n) Lower row: HAQ-DI change from baseline
a) No imputation was applied to missing data.
b) A linear mixed-effect model with repeated measures including treatment, visit, treatment-by-visit interaction, baseline value, and site as fixed effects and subject as a random effect, assuming a compound symmetry covariance structure

The primary endpoint (3) of the rate of DAS28-4 (ESR) <2.6 at Month 6 was 2.70% (4 of 148 subjects) in the placebo group, 9.13% (24 of 263 subjects) in the tofacitinib 5 mg group, and 13.33% (36 of 270 subjects) in the tofacitinib 10 mg group and as shown in Table 34, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo.

Table 34. Rate of DAS28-4 (ESR) <2.6 at Month 6 (FAS, NRI[a])

Placebo + DMARD	Tofacitinib + DMARD		Difference from placebo [95% CI][b], *P*-value[b]	
	Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 5 mg	Tofacitinib 10 mg
2.70 (4/148)	9.13 (24/263)	13.33 (36/270)	6.42 [2.07, 10.77] *P* = 0.0038	10.63 [5.80, 15.45] *P* < 0.0001

% (n)
a) Non-responder imputation (NRI) method: Patients with missing values (patients advanced to tofacitinib and non-responders at Month 3, patients withdrawn prior to Month 6) were treated as failures.
b) Normal approximation was used.

Adverse events in 0 to 3 months occurred in 52.7% of the tofacitinib 5 mg group (166 of 315 subjects), 54.4% of the tofacitinib 10 mg group (173 of 318 subjects), and 61.0% of the placebo group (97 of 159 subjects) and the main events were as shown in Table 35.

Adverse events in 3 to 6 months occurred in 38.4% of the tofacitinib 5 mg group (121 of 315 subjects), 39.0% of the tofacitinib 10 mg group (124 of 318 subjects), 25.9% of the placebo group (21 of 81 subjects), 42.1% of the placebo→tofacitinib 5 mg group (16 of 38 subjects), and 45.0% of the placebo→tofacitinib 10 mg group (18 of 40 subjects) and the main events were upper respiratory tract infection (tofacitinib 5 mg group, 4.1% [13 of 315 subjects]; tofacitinib 10 mg group, 2.8% [9 of 318 subjects]; placebo→tofacitinib 5 mg group, 2.6% [1 of 38 subjects]; placebo→tofacitinib 10 mg group, 7.5% [3 of 40 subjects]) and peripheral oedema (tofacitinib 5 mg group, 1.3% [4 of 315 subjects]; tofacitinib 10 mg group, 2.5% [8 of 318 subjects]; placebo group, 1.2% [1 of 81 subjects]; placebo→tofacitinib 5 mg group, 7.9% [3 of 38 subjects]) etc.

Adverse events in >6 months occurred in 33.0% of the tofacitinib 5 mg group (104 of 315 subjects), 42.5% of the tofacitinib 10 mg group (135 of 318 subjects), 43.0% of the placebo→tofacitinib 5 mg group (34 of 79 subjects), and 36.3% of the placebo→tofacitinib 10 mg group (29 of 80 subjects) and the most commonly reported event was upper respiratory tract infection (tofacitinib 5 mg group, 3.5% [11 of 315 subjects]; tofacitinib 10 mg group, 5.7% [18 of 318 subjects]; placebo→tofacitinib 5 mg group, 3.8% [3 of 79 subjects]; placebo→tofacitinib 10 mg group, 3.8% [3 of 80 subjects]).

Table 35. Adverse events reported by at least 2% of subjects in any group (0-3 months, Safety analysis set)

Event	Placebo (n = 159)	Tofacitinib 5 mg (n = 315)	Tofacitinib 10 mg (n = 318)
Upper respiratory tract infection	7 (4.4)	19 (6.0)	23 (7.2)
Diarrhoea	6 (3.8)	14 (4.4)	10 (3.1)
Nasopharyngitis	12 (7.5)	16 (5.1)	7 (2.2)
Headache	6 (3.8)	12 (3.8)	10 (3.1)
Nausea	4 (2.5)	11 (3.5)	8 (2.5)
Gastritis	3 (1.9)	8 (2.5)	6 (1.9)
Dyspepsia	2 (1.3)	4 (1.3)	8 (2.5)
Back pain	0	4 (1.3)	8 (2.5)
ALT increased	4 (2.5)	6 (1.9)	6 (1.9)
Hypertension	1 (0.6)	4 (1.3)	7 (2.2)
Bronchitis	4 (2.5)	7 (2.2)	3 (0.9)
Anaemia	3 (1.9)	7 (2.2)	2 (0.6)
Vomiting	3 (1.9)	7 (2.2)	2 (0.6)
Pharyngitis	5 (3.1)	3 (1.0)	5 (1.6)
Rheumatoid arthritis	6 (3.8)	3 (1.0)	2 (0.6)

n (%)

Two deaths occurred in the tofacitinib 5 mg group (traumatic brain damage/intracranial haemorrhage, rheumatoid arthritis/duodenal ulcer haemorrhage) and two in the tofacitinib 10 mg group (pulmonary hypertension/respiratory failure, acute cardiac failure) and a causal relationship to study drug could not be denied for the one death in the tofacitinib 10 mg group (pulmonary hypertension/respiratory failure). Serious adverse events were reported by 21 subjects in the tofacitinib 5 mg group, 24 subjects in the tofacitinib 10 mg group, 7 subjects in the placebo→tofacitinib 5 mg group, and 1 subject in the placebo→tofacitinib 10 mg group and the main events were as shown in Table 36. Adverse events leading to discontinuation were reported by 20 subjects in the tofacitinib 5 mg group, 29 subjects in the tofacitinib 10 mg group, 3 subjects in the placebo group, and 2 subjects in the placebo→tofacitinib 10 mg group.

Table 36. Serious adverse events reported by at least 2 subjects in the study (Safety analysis set)

Event	Tofacitinib 5 mg (n = 315)	Tofacitinib 10 mg (n = 318)	Placebo→ Tofacitinib 5 mg (n = 79)	Placebo→ Tofacitinib 10 mg (n = 80)
Chest pain	2	1	1	0
Rheumatoid arthritis	2	0	2	0
Osteoarthritis	1	0	1	0
Pneumonia	0	2	0	0
Pulmonary tuberculosis	0	2	0	0
Tendon rupture	0	2	0	0

n

Adverse drug reactions in 0 to 3 months occurred in 35.2% of the tofacitinib 5 mg group (111 of 315 subjects), 35.8% of the tofacitinib 10 mg group (114 of 318 subjects), and 31.4% of the placebo group (50 of 159 subjects), adverse drug reactions in 3 to 6 months occurred in 20.3% of the tofacitinib 5 mg group (64 of 315 subjects), 20.1% of the tofacitinib 10 mg group (64 of 318 subjects), 11.1% of the placebo group (9 of 81 subjects), 23.7% of the placebo→tofacitinib 5 mg group (9 of 38 subjects), and 32.5% of the placebo→tofacitinib 10 mg group (13 of 40 subjects), and adverse drug reactions in >6 months occurred in 16.8% of the tofacitinib 5 mg group (53 of 315 subjects), 23.0% of the tofacitinib 10 mg group (73 of 318 subjects), 22.8% of the placebo→tofacitinib 5 mg group (18 of 79 subjects), and 22.5% of the placebo→tofacitinib 10 mg group (18 of 80 subjects).

4.(iii).A.(3).5) Phase III study in RA patients who had an inadequate response to MTX (5.3.5.1.4, Study A3921064 [May 2009 to March 2011])

A placebo- and adalimumab-controlled, randomized, double-blind, parallel-group, comparative study in foreign RA patients who had an inadequate response to MTX[36] (Target number of cases of 700 [200 subjects each for the tofacitinib 5 mg, 10 mg, and adalimumab groups, 50 subjects each for the placebo→tofacitinib 5 mg and placebo→tofacitinib 10 mg groups]) was conducted to evaluate the efficacy and safety of tofacitinib in combination with MTX.

Subjects were to receive tofacitinib 5 or 10 mg BID orally, placebo, or adalimumab 40 mg subcutaneous injection every other week, added to background MTX. The duration of treatment was 12 months. Subjects were to continue to receive a stable dosage of MTX.

The study consisted of two periods (up to Month 6, the double-blind placebo-controlled period; after Month 6, the double-blind active extension period) and subjects randomized to placebo (the placebo→tofacitinib 5 mg group and the placebo→tofacitinib 10 mg group) who were determined to be non-responders[37] at Month 3 were advanced in a double-blind fashion to tofacitinib 5 or 10 mg and all placebo subjects were advanced in a double-blind fashion to tofacitinib 5 or 10 mg at Month 6. In all of the placebo, tofacitinib, and adalimumab groups, if subjects were determined to be non-responders at Month 3, their subsequent efficacy data were treated as missing values and imputed.

The study had 3 primary efficacy endpoints: (1) ACR20 response rate at Month 6, (2) the mean change from baseline in HAQ-DI at Month 3, and (3) the rate of DAS28-4 (ESR) <2.6 at Month 6. A sequential gatekeeping or step-down testing procedure was planned to adjust for multiplicity from a total of 6 pairwise comparisons for 3 primary endpoints and two dose levels of tofacitinib and placebo. All pairwise comparisons were performed at a two-sided significance level of 5%. A pairwise comparison of tofacitinib 10 mg and placebo for a given endpoint could be performed only if tofacitinib 10 mg at the prior endpoint was statistically significant. A pairwise comparison of tofacitinib 5 mg and placebo for a given endpoint could be performed only if both tofacitinib 10 mg at the same endpoint, and tofacitinib 5 mg at the prior endpoint were statistically significant. For efficacy analyses of tofacitinib vs. placebo (up to Month 3), the placebo→tofacitinib 5 mg group and the placebo→tofacitinib 10 mg group were pooled and treated as a placebo group.

Seven hundred seventeen randomized subjects (204 subjects in the tofacitinib 5 mg group, 201 subjects in the tofacitinib 10 mg group, 56 subjects in the placebo→tofacitinib 5 mg group, 52 subjects in the placebo→tofacitinib 10 mg group, 204 subjects in the adalimumab group) were included in the FAS and the safety analysis set, and included in the efficacy analyses. Withdrawals occurred in 26.5% of the tofacitinib 5 mg group (54 of 204 subjects), 21.4% of the tofacitinib 10 mg group (43 of 201 subjects), 16.1% of the placebo→tofacitinib 5 mg group (9 of 56 subjects), 25.0% of the placebo→tofacitinib 10 mg group (13 of 52 subjects), and 20.6% of the adalimumab group (42 of 204 subjects) and the main reasons for withdrawals were

[36] Key inclusion criteria: patients who had a diagnosis of RA based upon the American College of Rheumatology criteria and active disease, fulfilling the following criteria: (a) patients had been taking MTX continuously for ≥4 months and on a stable dosage (7.5-25 mg/week) for ≥6 weeks prior to the first dose of study drug, (b) ≥6 tender/painful joints and ≥6 swollen joints, and (c) CRP >7 mg/L or erythrocyte sedimentation rate (ESR) >28 mm/hr.
[37] Patients who failed to achieve a minimum improvement of at least 20% reduction in both swollen and tender/painful joint counts over baseline

adverse events (tofacitinib 5 mg group, 11.8% [24 of 204 subjects]; tofacitinib 10 mg group, 11.9% [24 of 201 subjects]; placebo→tofacitinib 5 mg group, 3.6% [2 of 56 subjects]; placebo→tofacitinib 10 mg group, 9.6% [5 of 52 subjects]; adalimumab group, 10.8% [22 of 204 subjects]) etc. The proportions of subjects who were determined to be non-responders and advanced from placebo to tofacitinib at Month 3 were 50.0% (28 of 56 subjects) in the placebo→tofacitinib 5 mg group and 40.4% (21 of 52 subjects) in the placebo→tofacitinib 10 mg group. In the tofacitinib 5 mg, 10 mg, and adalimumab groups, the proportions of subjects who were determined to be non-responders at Month 3 were 24.5% (50 of 204 subjects), 23.4% (47 of 201 subjects), and 28.4% (58 of 204 subjects), respectively.

The primary endpoint (1) of ACR20 response rate at Month 6 was 28.30% (30 of 106 subjects) in the placebo group, 51.53% (101 of 196 subjects) in the tofacitinib 5 mg group, 52.55% (103 of 196 subjects) in the tofacitinib 10 mg group, and 47.24% (94 of 199 subjects) in the adalimumab group and as shown in Table 37, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo. The secondary endpoints of ACR50 and ACR70 response rates at Month 6 were as shown in Table 37.

Table 37. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Month 6 (FAS, NRI[a])

	Placebo + MTX	Tofacitinib 5 mg + MTX	Tofacitinib 10 mg + MTX	Adalimumab + MTX	Difference from placebo [95% CI][b], *P*-value[b]		
					Tofacitinib 5 mg + MTX	Tofacitinib 10 mg + MTX	Adalimumab + MTX
ACR20 response rate	28.30 (30/106)	51.53 (101/196)	52.55 (103/196)	47.24 (94/199)	23.22 [12.16, 34.29] *P* < 0.0001	24.24 [13.18, 35.31] *P* < 0.0001	18.93 [7.90, 29.96]
ACR50 response rate	12.26 (13/106)	36.73 (72/196)	34.69 (68/196)	27.64 (55/199)	24.47 [15.27, 33.66]	22.42 [13.29, 31.56]	15.37 [6.56, 24.18]
ACR70 response rate	1.89 (2/106)	19.90 (39/196)	21.94 (43/196)	9.05 (18/199)	18.01 [11.85, 24.17]	20.05 [13.70, 26.39]	7.15 [2.40, 11.91]

% (n)
a) Non-responder imputation (NRI) method: Patients with missing values (patients advanced to tofacitinib and non-responders at Month 3, patients withdrawn prior to Month 6) were treated as failures.
b) Normal approximation was used.

The primary endpoint (2) of the change from baseline in HAQ-DI at Month 3 (mean ± SD) was −0.17 ± 0.56 in the placebo group, −0.49 ± 0.59 in the tofacitinib 5 mg group, −0.59 ± 0.58 in the tofacitinib 10 mg group, and −0.45 ± 0.52 in the adalimumab group and as shown in Table 38, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo.

Table 38. HAQ-DI over time and changes from baseline (FAS[a])

	Placebo + MTX	Tofacitinib 5 mg + MTX	Tofacitinib 10 mg + MTX	Adalimumab + MTX
Baseline	1.42 ± 0.68 (106)	1.50 ± 0.64 (201)	1.53 ± 0.63 (199)	1.50 ± 0.59 (201)
Month 1	1.32 ± 0.69 (106) -0.10 ± 0.40	1.15 ± 0.66 (194) -0.34 ± 0.53	1.11 ± 0.67 (196) -0.41 ± 0.49	1.12 ± 0.64 (198) -0.37 ± 0.48
Month 3	1.25 ± 0.67 (99) -0.17 ± 0.56	1.00 ± 0.72 (188) -0.49 ± 0.59	0.94 ± 0.75 (185) -0.59 ± 0.58	1.05 ± 0.64 (190) -0.45 ± 0.52
Difference from placebo at Month 3 [95% CI][b] *P*-value[b]	-	-0.31 [-0.43, -0.19] *P* < 0.0001	-0.38 [-0.50, -0.25] *P* < 0.0001	-0.25 [-0.37, -0.13]

Mean ± SD (n) Lower row: HAQ-DI change from baseline
a) No imputation was applied to missing data.
b) A linear mixed-effect model with repeated measures including treatment, visit, treatment-by-visit interaction, baseline value, and site as fixed effects and subject as a random effect, assuming a compound symmetry covariance structure

The primary endpoint (3) of the rate of DAS28-4 (ESR) <2.6 at Month 6 was 1.09% (1 of 92 subjects) in the placebo group, 6.21% (11 of 177 subjects) in the tofacitinib 5 mg group, 12.50% (22 of 176 subjects) in the

tofacitinib 10 mg group, and 6.74% (12 of 178 subjects) in the adalimumab group and as shown in Table 39, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo.

Table 39. Rate of DAS28-4 (ESR) <2.6 at Month 6 (FAS, NRI[a])

Placebo + MTX	Tofacitinib 5 mg + MTX	Tofacitinib 10 mg + MTX	Adalimumab + MTX	Difference from placebo [95% CI] [b], *P*-value[b]		
				Tofacitinib 5 mg + MTX	Tofacitinib 10 mg + MTX	Adalimumab + MTX
1.09 (1/92)	6.21 (11/177)	12.50 (22/176)	6.74 (12/178)	5.12 [0.98, 9.26] *P* = 0.0151	11.41 [6.08, 16.73] *P* < 0.0001	5.65 [1.40, 9.90]

% (n)
a) Non-responder imputation (NRI) method: Patients with missing values (patients advanced to tofacitinib and non-responders at Month 3, patients withdrawn prior to Month 6) were treated as failures.
b) Normal approximation was used.

Adverse events in 0 to 3 months occurred in 52.0% of the tofacitinib 5 mg group (106 of 204 subjects), 46.8% of the tofacitinib 10 mg group (94 of 201 subjects), 51.5% of the adalimumab group (105 of 204 subjects), and 47.2% of the placebo group (51 of 108 subjects) and the main events were as shown in Table 40.

Adverse events in 3 to 6 months occurred in 32.8% of the tofacitinib 5 mg group (67 of 204 subjects), 30.8% of the tofacitinib 10 mg group (62 of 201 subjects), 33.3% of the adalimumab group (68 of 204 subjects), 27.1% of the placebo group (16 of 59 subjects), 25.0% of the placebo→tofacitinib 5 mg group (7 of 28 subjects), and 42.9% of the placebo→tofacitinib 10 mg group (9 of 21 subjects) and the main events were urinary tract infection (tofacitinib 5 mg group, 2.0% [4 of 204 subjects]; adalimumab group, 2.9% [6 of 204 subjects]; placebo→tofacitinib 5 mg group, 3.6% [1 of 28 subjects]; placebo→tofacitinib 10 mg group, 4.8% [1 of 21 subjects]) and nasopharyngitis (tofacitinib 5 mg group, 2.5% [5 of 204 subjects]; tofacitinib 10 mg group, 1.0% [2 of 201 subjects]; adalimumab group, 1.5% [3 of 204 subjects]; placebo group, 1.7% [1 of 59 subjects]) etc.

Adverse events in >6 months occurred in 43.6% of the tofacitinib 5 mg group (89 of 204 subjects), 41.8% of the tofacitinib 10 mg group (84 of 201 subjects), 40.7% of the adalimumab group (83 of 204 subjects), 32.1% of the placebo→tofacitinib 5 mg group (18 of 56 subjects), and 40.4% of the placebo→tofacitinib 10 mg group (21 of 52 subjects) and the main events were bronchitis (tofacitinib 5 mg group, 2.5% [5 of 204 subjects]; tofacitinib 10 mg group, 4.0% [8 of 201 subjects]; adalimumab group, 2.0% [4 of 204 subjects]; placebo→tofacitinib 5 mg group, 3.6% [2 of 56 subjects]; placebo→tofacitinib 10 mg group, 3.8% [2 of 52 subjects]) and upper respiratory tract infection (tofacitinib 5 mg group, 3.9% [8 of 204 subjects]; tofacitinib 10 mg group, 2.5% [5 of 201 subjects]; adalimumab group, 2.0% [4 of 204 subjects]; placebo→tofacitinib 5 mg group, 1.8% [1 of 56 subjects]; placebo→tofacitinib 10 mg group, 1.9% [1 of 52 subjects]) etc.

Table 40. Adverse events reported by at least 2% of subjects in any group (0-3 months, Safety analysis set)

Event	Placebo (n = 108)	Tofacitinib 5 mg (n = 204)	Tofacitinib 10 mg (n = 201)	Adalimumab (n = 204)
Upper respiratory tract infection	1 (0.9)	9 (4.4)	7 (3.5)	7 (3.4)
Headache	2 (1.9)	8 (3.9)	6 (3.0)	5 (2.5)
Nasopharyngitis	0	8 (3.9)	4 (2.0)	7 (3.4)
Hypertension	2 (1.9)	2 (1.0)	6 (3.0)	0
Urinary tract infection	0	5 (2.5)	3 (1.5)	7 (3.4)
Diarrhoea	0	5 (2.5)	2 (1.0)	2 (1.0)
Peripheral oedema	3 (2.8)	3 (1.5)	4 (2.0)	3 (1.5)
ALT increased	0	3 (1.5)	4 (2.0)	1 (0.5)
Dyspepsia	2 (1.9)	4 (2.0)	3 (1.5)	3 (1.5)
Herpes zoster	0	0	6 (3.0)	0
Upper abdominal pain	1 (0.9)	4 (2.0)	2 (1.0)	3 (1.5)
Blood creatine phosphokinase increased	1 (0.9)	1 (0.5)	4 (2.0)	1 (0.5)
Bronchitis	1 (0.9)	2 (1.0)	3 (1.5)	4 (2.0)
Vomiting	1 (0.9)	4 (2.0)	0	0
Rheumatoid arthritis	2 (1.9)	4 (2.0)	0	1 (0.5)
Rash	1 (0.9)	1 (0.5)	3 (1.5)	4 (2.0)
Arthralgia	1 (0.9)	2 (1.0)	1 (0.5)	4 (2.0)
Cough	3 (2.8)	0	2 (1.0)	4 (2.0)

n (%)

One death each occurred in the tofacitinib 5 mg group (pneumonia) and the adalimumab group (cardiac arrest) and a causal relationship to study drug could not be denied for the one death in the tofacitinib 5 mg group (pneumonia). Serious adverse events were reported by 32 subjects in the tofacitinib 5 mg group, 22 subjects in the tofacitinib 10 mg group, 20 subjects in the adalimumab group, 3 subjects in the placebo→tofacitinib 5 mg group, and 7 subjects in the placebo→tofacitinib 10 mg group and the main events were as shown in Table 41. Adverse events leading to discontinuation were reported by 24 subjects in the tofacitinib 5 mg group, 24 subjects in the tofacitinib 10 mg group, 21 subjects in the adalimumab group, 4 subjects in the placebo group, 1 subject in the placebo→tofacitinib 5 mg group, and 2 subjects in the placebo→tofacitinib 10 mg group.

Table 41. Serious adverse events reported by at least 2 subjects in the study (Safety analysis set)

Event	Tofacitinib 5 mg (n = 204)	Tofacitinib 10 mg (n = 201)	Placebo → Tofacitinib 5 mg (n = 56)	Placebo → Tofacitinib 10 mg (n = 52)	Adalimumab (n = 204)
Humerus fracture	2	0	0	0	0
Cellulitis	2	1	0	0	1
Tendon rupture	1	1	0	0	0
Pneumonia	2	1	0	0	0
Femur fracture	1	1	0	0	1
Myocardial infarction	1	1	0	0	1
Herpes zoster	1	1	0	0	0
Non-small cell lung cancer	1	0	0	0	1
Cholelithiasis	1	0	0	1	0
Pulmonary tuberculosis	0	2	0	0	0

n

Adverse drug reactions in 0 to 3 months occurred in 32.4% of the tofacitinib 5 mg group (66 of 204 subjects), 26.4% of the tofacitinib 10 mg group (53 of 201 subjects), 26.5% of the adalimumab group (54 of 204 subjects), and 17.6% of the placebo group (19 of 108 subjects), adverse drug reactions in 3 to 6 months occurred in 14.7% of the tofacitinib 5 mg group (30 of 204 subjects), 12.9% of the tofacitinib 10 mg group (26 of 201 subjects), 17.2% of the adalimumab group (35 of 204 subjects), 10.2% of the placebo group (6 of 59 subjects), 14.3% of the placebo→tofacitinib 5 mg group (4 of 28 subjects), and 19.0% of the placebo→tofacitinib 10 mg group (4 of 21 subjects), and adverse drug reactions in >6 months occurred in 22.1% of the tofacitinib 5 mg

group (45 of 204 subjects), 17.4% of the tofacitinib 10 mg group (35 of 201 subjects), 14.2% of the adalimumab group (29 of 204 subjects), 10.7% of the placebo→tofacitinib 5 mg group (6 of 56 subjects), and 21.2% of the placebo→tofacitinib 10 mg group (11 of 52 subjects).

4.(iii).A.(3).6) Phase III study in RA patients who had an inadequate response to TNF inhibitor (5.3.5.1.1, Study A3921032 [October 2009 to March 2011])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study in foreign RA patients who had an inadequate response to TNF inhibitor[38] (Target number of cases of 396 [132 subjects each for the tofacitinib 5 mg and 10 mg groups, 66 subjects each for the placebo→tofacitinib 5 mg and placebo→tofacitinib 10 mg groups]) was conducted to evaluate the efficacy and safety of tofacitinib in combination with MTX.

Subjects were to receive tofacitinib 5 or 10 mg BID orally or placebo, added to background MTX. The duration of treatment was 6 months. Subjects randomized to placebo were advanced in a double-blind fashion to tofacitinib 5 or 10 mg at Month 3 (the placebo→tofacitinib 5 mg group and the placebo→tofacitinib 10 mg group). Subjects were to continue to receive a stable dosage of MTX.

The study had 3 primary efficacy endpoints: (1) ACR20 response rate at Month 3, (2) the mean change from baseline in HAQ-DI at Month 3, and (3) the rate of DAS28-4 (ESR) <2.6 at Month 3. A sequential gatekeeping or step-down testing procedure was planned to adjust for multiplicity from a total of 6 pairwise comparisons for 3 primary endpoints and two dose levels of tofacitinib and placebo. All pairwise comparisons were performed at a two-sided significance level of 5%. A pairwise comparison of tofacitinib 10 mg and placebo for a given endpoint could be performed only if tofacitinib 10 mg at the prior endpoint was statistically significant. A pairwise comparison of tofacitinib 5 mg and placebo for a given endpoint could be performed only if both tofacitinib 10 mg at the same endpoint, and tofacitinib 5 mg at the prior endpoint were statistically significant. For efficacy analyses of tofacitinib vs. placebo (up to Month 3), the placebo→tofacitinib 5 mg group and the placebo→tofacitinib 10 mg group were pooled and treated as a placebo group.

All of 399 randomized subjects (133 subjects in the tofacitinib 5 mg group, 134 subjects in the tofacitinib 10 mg group, 66 subjects in the placebo→tofacitinib 5 mg group, 66 subjects in the placebo→tofacitinib 10 mg) were included in the FAS and the safety analysis set, and included in the efficacy analyses. Withdrawals occurred in 19.5% of the tofacitinib 5 mg group (26 of 133 subjects), 23.1% of the tofacitinib 10 mg group (31 of 134 subjects), 19.7% of the placebo→tofacitinib 5 mg group (13 of 66 subjects), and 27.3% of the placebo→tofacitinib 10 mg group (18 of 66 subjects) and the main reasons for withdrawals were adverse events (tofacitinib 5 mg group, 9.0% [12 of 133 subjects]; tofacitinib 10 mg group, 9.0% [12 of 134 subjects]; placebo→tofacitinib 5 mg group, 6.1% [4 of 66 subjects]; placebo→tofacitinib 10 mg group, 6.1% [4 of 66 subjects]) and lack of efficacy (tofacitinib 5 mg group, 1.5% [2 of 133 subjects]; tofacitinib 10 mg group, 3.7% [5 of 134 subjects]; placebo→tofacitinib 5 mg group, 4.5% [3 of 66 subjects]; placebo→tofacitinib 10 mg group, 12.1% [8 of 66 subjects]) etc.

[38] Key inclusion criteria: patients who had a diagnosis of RA based upon the American College of Rheumatology criteria and active disease, fulfilling the following criteria: (a) patients had had an inadequate response to at least 1 TNF inhibitor, (b) patients had been taking MTX continuously for ≥4 months and on a stable dosage (7.5-25 mg/week) for ≥6 weeks prior to the first dose of study drug, (c) ≥6 tender/painful joints and ≥6 swollen joints, and (d) CRP >7 mg/L or ESR >28 mm/hr.

The primary endpoint (1) of ACR20 response rate at Month 3 was 24.43% (32 of 131 subjects) in the placebo group, 41.67% (55 of 132 subjects) in the tofacitinib 5 mg group, and 48.12% (64 of 133 subjects) in the tofacitinib 10 mg group and as shown in Table 42, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo. The secondary endpoints of ACR50 and ACR70 response rates at Month 3 were as shown in Table 42.

Table 42. ACR20 (primary endpoint), ACR50, and ACR70 response rates at Month 3 (FAS, NRI[a])

	Placebo + MTX	Tofacitinib + MTX		Difference from placebo [95% CI][b], *P*-value[b]	
		Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 5 mg	Tofacitinib 10 mg
ACR20 response rate	24.43 (32/131)	41.67 (55/132)	48.12 (64/133)	17.23 [6.06, 28.41] *P* = 0.0024	23.69 [12.45, 34.92] *P* < 0.0001
ACR50 response rate	8.40 (11/131)	26.52 (35/132)	27.82 (37/133)	18.11 [9.21, 27.02]	19.42 [10.44, 28.39]
ACR70 response rate	1.53 (2/131)	13.64 (18/132)	10.53 (14/133)	12.10 [5.89, 18.32]	8.99 [3.37, 14.62]

% (n)
a) Non-responder imputation (NRI) method: Patients with missing values were treated as failures.
b) Normal approximation was used.

The primary endpoint (2) of the change from baseline in HAQ-DI at Month 3 (mean ± SD) was −0.17 ± 0.41 in the placebo group, −0.41 ± 0.52 in the tofacitinib 5 mg group, and −0.41 ± 0.52 in the tofacitinib 10 mg group and as shown in Table 43, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo.

Table 43. HAQ-DI over time and changes from baseline (FAS[a])

	Placebo + MTX	Tofacitinib 5 mg + MTX	Tofacitinib 10 mg + MTX
Baseline	1.63 ± 0.66 (132)	1.60 ± 0.66 (132)	1.50 ± 0.61 (134)
Week 2	1.50 ± 0.69 (125) -0.12 ± 0.34	1.38 ± 0.71 (130) -0.21 ± 0.35	1.28 ± 0.58 (128) -0.21 ± 0.40
Month 1	1.38 ± 0.72 (123) -0.22 ± 0.39	1.37 ± 0.68 (123) -0.25 ± 0.46	1.19 ± 0.65 (123) -0.32 ± 0.44
Month 3	1.44 ± 0.72 (118) -0.17 ± 0.41	1.20 ± 0.72 (118) -0.41 ± 0.52	1.10 ± 0.66 (125) -0.41 ± 0.52
Difference from placebo at Month 3 [95% CI][b] *P*-value[b]	-	-0.25 [-0.36, -0.15] *P* < 0.0001	-0.28 [-0.38, -0.17] *P* < 0.0001

Mean ± SD (n) Lower row: HAQ-DI change from baseline
a) No imputation was applied to missing data.
b) A linear mixed-effect model with repeated measures including treatment, visit, treatment-by-visit interaction, baseline value, and site as fixed effects and subject as a random effect, assuming a compound symmetry covariance structure

The primary endpoint (3) of the rate of DAS28-4 (ESR) <2.6 at Month 3 was 1.67% (2 of 120 subjects) in the placebo group, 6.72% (8 of 119 subjects) in the tofacitinib 5 mg group, and 8.80% (11 of 125 subjects) in the tofacitinib 10 mg group and as shown in Table 44, pairwise comparisons showed statistically significant differences between each dose of tofacitinib and placebo.

Table 44. Rate of DAS28-4 (ESR) <2.6 at Month 3 (FAS, NRI[a])

Placebo + MTX	Tofacitinib + MTX		Difference from placebo [95% CI][b], *P*-value[b]	
	Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 5 mg	Tofacitinib 10 mg
1.67 (2/120)	6.72 (8/119)	8.80 (11/125)	5.05 [0.00, 10.10] *P* = 0.0496	7.13 [1.66, 12.60] *P* = 0.0105

% (n)
a) Non-responder imputation (NRI) method: Patients with missing values were treated as failures.
b) Normal approximation was used.

Adverse events in 0 to 3 months occurred in 53.4% of the tofacitinib 5 mg group (71 of 133 subjects), 56.7% of the tofacitinib 10 mg group (76 of 134 subjects), and 56.8% of the placebo group (75 of 132 subjects) and the main events were as shown in Table 45.

Adverse events in 3 to 6 months occurred in 42.9% of the tofacitinib 5 mg group (57 of 133 subjects), 43.3%

of the tofacitinib 10 mg group (58 of 134 subjects), 36.4% of the placebo→tofacitinib 5 mg group (24 of 66 subjects), and 42.4% of the placebo→tofacitinib 10 mg group (28 of 66 subjects) and the main events were upper respiratory tract infection (tofacitinib 5 mg group, 2.3% [3 of 133 subjects]; tofacitinib 10 mg group, 5.2% [7 of 134 subjects]; placebo→tofacitinib 5 mg group, 3.0% [2 of 66 subjects]; placebo→tofacitinib 10 mg group, 1.5% [1 of 66 subjects]) and nasopharyngitis (tofacitinib 5 mg group, 3.8% [5 of 133 subjects]; tofacitinib 10 mg group, 3.7% [5 of 134 subjects]; placebo→tofacitinib 5 mg group, 1.5% [1 of 66 subjects]) etc.

Table 45. Adverse events reported by at least 2% of subjects in any group (0-3 months, Safety analysis set)

Event	Placebo (n = 132)	Tofacitinib 5 mg (n = 133)	Tofacitinib 10 mg (n = 134)
Diarrhoea	5 (3.8)	8 (6.0)	5 (3.7)
Nasopharyngitis	4 (3.0)	5 (3.8)	6 (4.5)
Headache	1 (0.8)	3 (2.3)	8 (6.0)
Urinary tract infection	3 (2.3)	5 (3.8)	3 (2.2)
Upper respiratory tract infection	4 (3.0)	5 (3.8)	2 (1.5)
Nausea	9 (6.8)	4 (3.0)	2 (1.5)
Rheumatoid arthritis	4 (3.0)	3 (2.3)	1 (0.7)
Constipation	1 (0.8)	4 (3.0)	3 (2.2)
Back pain	2 (1.5)	3 (2.3)	3 (2.2)
Peripheral oedema	5 (3.8)	3 (2.3)	1 (0.7)
Cough	5 (3.8)	3 (2.3)	0
Depression	1 (0.8)	2 (1.5)	4 (3.0)
Arthralgia	5 (3.8)	1 (0.8)	1 (0.7)
Sinusitis	4 (3.0)	1 (0.8)	1 (0.7)
Hypertension	1 (0.8)	1 (0.8)	3 (2.2)
Paraesthesia	3 (2.3)	0	1 (0.7)
Upper abdominal pain	0	3 (2.3)	1 (0.7)
Fatigue	0	1 (0.8)	3 (2.2)
Skin lesion	0	1 (0.8)	3 (2.2)
Muscle spasms	3 (2.3)	0	1 (0.7)
Haematuria	3 (2.3)	0	0
Muscle strain	0	0	3 (2.2)
Blood creatine phosphokinase increased	0	0	3 (2.2)

n (%)

One death occurred in the placebo→tofacitinib 10 mg group (pulmonary embolism), but its causal relationship to study drug was denied. Serious adverse events were reported by 6 subjects in the tofacitinib 5 mg group (pancreatitis, mental disorder, back pain, cerebrovascular accident, panniculitis, and bronchopneumonia [1 subject each]), 8 subjects in the tofacitinib 10 mg group (ulcerative keratitis, pyelonephritis, pericarditis, pulmonary embolism, vomiting/nausea/anaemia, cholelithiasis, acute renal failure/diverticulitis, and aortic aneurysm [1 subject each]), 5 subjects in the placebo→tofacitinib 5 mg group (cerebrovascular accident, gastroenteritis, contusion/foot fracture/joint sprain, transient cerebrovascular events/hypertension, and aspiration pneumonia [1 subject each]), and 5 subjects in the placebo→tofacitinib 10 mg group (Goodpasture's syndrome, dehydration, anaemia/hyponatraemia/interstitial lung disease, ineffective drug/spontaneous abortion/pregnancy, and pulmonary embolism [1 subject each]). Adverse events leading to discontinuation were reported by 12 subjects in the tofacitinib 5 mg group, 12 subjects in the tofacitinib 10 mg group, 4 subjects in the placebo→tofacitinib 5 mg group, and 4 subjects in the placebo→tofacitinib 10 mg group.

Adverse drug reactions in 0 to 3 months occurred in 25.6% of the tofacitinib 5 mg group (34 of 133 subjects), 32.8% of the tofacitinib 10 mg group (44 of 134 subjects), and 19.7% of the placebo group (26 of 132 subjects) and adverse drug reactions in 3 to 6 months occurred in 18.8% of the tofacitinib 5 mg group (25 of 133 subjects), 21.6% of the tofacitinib 10 mg group (29 of 134 subjects), 18.2% of the placebo→tofacitinib 5 mg group (12 of 66 subjects), and 13.6% of the placebo→tofacitinib 10 mg group (9 of 66 subjects).

4.(iii).A.(3).7) Phase II study with atorvastatin in RA patients treated with tofacitinib (5.3.4.2.1, Study A3921109 [February to November 2010])

A placebo-controlled, randomized, double-blind, parallel-group, comparative study was conducted to assess the effects of atorvastatin on lipid changes in foreign RA patients[39] treated with tofacitinib (Target number of cases of 100 [50 cases per group]).

Subjects were to receive tofacitinib 10 mg BID orally for 6 weeks in an open-label manner (the open-label period) and then atorvastatin 10 mg QD or placebo in addition to tofacitinib 10 mg BID orally for 6 weeks in a double-blind manner (the double-blind period).

All of 111 subjects who received tofacitinib during the open-label period were included in the safety analysis set, of whom, all 97 subjects who were randomized and received atorvastatin or placebo (50 subjects in the atorvastatin group, 47 subjects in the placebo group) were included in the FAS and the efficacy analyses. The withdrawal rates were 11.7% (13 of 111 subjects) during the open-label period and 6.0% (3 of 50 subjects) in the atorvastatin group and 4.3% (2 of 47 subjects) in the placebo group during the double-blind period and the main reasons for withdrawals were adverse events (open-label period, 6.3% [7 of 111 subjects]; atorvastatin group, 6.0% [3 of 50 subjects]; placebo group, 6.4% [3 of 47 subjects]) etc.

The primary efficacy endpoint of the percent change in LDL-cholesterol from baseline (Week 6) to Week 12 (least-square mean ± standard error [SE]) was −35.34 ± 2.25% in the atorvastatin group and 5.80 ± 2.27% in the placebo group and the addition of atorvastatin induced a statistically significant reduction compared with placebo (P <0.0001 [one-sided level of significance of 2.5%], a linear mixed-effect model with repeated measures including treatment, visit, treatment-by-visit interaction, and baseline value as fixed effects and subject as a random effect, assuming a compound symmetry covariance structure).

Adverse events occurred in 46.8% of subjects (52 of 111 subjects) during the open-label period and those reported by at least 2% of subjects were diarrhoea (2.7% [3 of 111 subjects]), nausea (3.6% [4 of 111 subjects]), herpes zoster (4.5% [5 of 111 subjects]), and headache (2.7% [3 of 111 subjects]). Adverse events occurred in 42.0% of the atorvastatin group (21 of 50 subjects) and 40.4% of the placebo group (19 of 47 subjects) during the double-blind period and the main events were peripheral oedema (atorvastatin group, 4.0% [2 of 50 subjects]; placebo group, 4.3% [2 of 47 subjects]) and upper respiratory tract infection (atorvastatin group, 4.0% [2 of 50 subjects]; placebo group, 4.3% [2 of 47 subjects]) etc.

No deaths were reported and serious adverse events were observed in 2 subjects (bacterial pneumonia, arthritis) during the open-label period and 1 subject (pneumonia) in the placebo group during the double-blind period and a causal relationship to study drug could not be denied for the 1 case of bacterial pneumonia during the open-label period. Adverse events leading to discontinuation were reported by 10 subjects during the open-

[39] Key inclusion criteria: patients who had a diagnosis of RA based upon the American College of Rheumatology criteria and active disease, fulfilling the following criteria: (a) ≥4 tender/painful joints and ≥4 swollen joints and (b) CRP >7 mg/L or ESR >28 mm/hr.

label period and 3 subjects in the atorvastatin group and 2 subjects in the placebo group during the double-blind period.

Adverse drug reactions occurred in 23.4% of subjects (26 of 111 subjects) during the open-label period and 10.0% of the atorvastatin group (5 of 50 subjects) and 17.0% of the placebo group (8 of 47 subjects) during the double-blind period.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Efficacy

The applicant filed a new drug application for tofacitinib for the proposed indications of "improvement in signs and symptoms of RA such as joint pain" "improvement in physical function," and "prevention of structural damage to joints." For the proposed indications of "improvement in signs and symptoms of RA such as joint pain" and "improvement in physical function," based on the ICH E5 guideline, the applicant planned to build a clinical data package containing foreign data (ACR response rate [a measure of improvement in signs and symptoms of RA such as joint pain] and HAQ-DI [a measure of improvement in physical function] data from foreign confirmatory studies, etc. [A3921045, A3921046, A3921064, etc.]) for submission in Japan: a Japanese phase II study (A3921040) was positioned as a bridging study and a foreign phase II study (A3921035) was positioned as a study to be bridged and if the bridging study was interpreted as capable of bridging the foreign data, the foreign data could be extrapolated to Japanese patients. For the proposed indication of "prevention of structural damage to joints," based on "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), Japanese patients also participated in a global phase III study (A3921044) that examined prevention of structural damage to joints as measured by mTSS changes and if consistent results were obtained between the entire population and the Japanese population, the study data were to be used as confirmatory study data for obtaining this indication in Japan.

4.(iii).B.(1).1) Effects in reducing signs and symptoms of RA such as joint pain

The applicant provided a justification for extrapolating foreign clinical data on the effects of tofacitinib on signs and symptoms of RA such as joint pain and evaluating the efficacy of tofacitinib in Japanese RA patients as follows:

The pharmacokinetic profile of tofacitinib was similar between Japanese and foreign subjects [see "4.(ii) Summary of clinical pharmacology studies"]. ACR20, ACR50, and ACR70 response rates at Week 12 in a Japanese phase II study (A3921040) and a foreign late phase II study (A3921035) were as shown in Table 46 and the response rates with ≥3 mg of tofacitinib in the Japanese phase II study were similar to or tended to be higher than those in the foreign late phase II study. The baseline demographic and disease characteristics of patients (the patient background) in the Japanese phase II and foreign late phase II studies were examined. As a result, there was a trend towards fewer tender/painful joints (Japanese phase II study, 13.6-18.6; foreign late phase II study, 24.1-27.1) and higher CRP (Japanese phase II study, 24.0-35.6; foreign late phase II study, 16.2-24.5) in the Japanese phase II study. The prior dose level of MTX was lower in the Japanese phase II study than in the foreign late phase II study (Japanese phase II study, 7.8 mg/week; foreign late phase II study, 13.6 mg/week) due to differences in the approved doses between Japan and overseas.[40] However, when a

[40] The approved doses of MTX in Japan at the time of conducting the Japanese phase II study were 6-8 mg/week. The approved doses in the US were

logistic regression analysis including the patient background, the use of biologics or MTX, or MTX dose as covariates was performed, none were identified as having a significant influence on ACR20 response rate at Week 12 and the differences in these factors were unlikely to affect efficacy evaluation. Furthermore, the occurrence of adverse events was mostly similar between the two studies [see "4.(iii).A *Summary of the submitted data*"]. Therefore, extrapolation of the foreign clinical data on the effects of tofacitinib on signs and symptoms of RA such as joint pain to Japanese patients is justified.

Table 46. ACR20, ACR50, and ACR70 response rates at Week 12
in Japanese phase II study (A3921040) and foreign late phase II study (A3921035) (FAS, LOCF)

	Placebo	Tofacitinib 1 mg	Tofacitinib 3 mg	Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 15 mg
ACR20 response rate						
Japanese phase II study (A3921040)	15.38 (8/52)	37.74 (20/53)	67.92 (36/53)	73.08 (38/52)	84.91 (45/53)	90.74 (49/54)
Foreign late phase II study (A3921035)	28.81 (17/59)	35.19 (19/54)	49.02 (25/51)	63.27 (31/49)	75.41 (46/61)	75.44 (43/57)
ACR50 response rate						
Japanese phase II study (A3921040)	7.69 (4/52)	13.21 (7/53)	26.42 (14/53)	46.15 (24/52)	69.81 (37/53)	72.22 (39/54)
Foreign late phase II study (A3921035)	11.86 (7/59)	14.81 (8/54)	25.49 (13/51)	40.82 (20/49)	49.18 (30/61)	54.39 (31/57)
ACR70 response rate						
Japanese phase II study (A3921040)	1.92 (1/52)	7.55 (4/53)	13.21 (7/53)	26.92 (14/52)	49.06 (26/53)	51.85 (28/54)
Foreign late phase II study (A3921035)	5.08 (3/59)	7.41 (4/54)	11.76 (6/51)	14.29 (7/49)	24.59 (15/61)	28.07 (16/57)

% (n)

A Japanese phase II study (A3921040) showed similar efficacy for the primary endpoint of ACR20 response rate for tofacitinib 3 mg and 5 mg. PMDA asked the applicant to provide a justification for not conducting a Japanese phase III confirmatory study evaluating doses including 3 mg and extrapolating the data from foreign phase III confirmatory studies at doses of 5 mg and 10 mg to Japanese patients.

The applicant explained as follows:
For foreign phase III confirmatory studies, a dose-response modeling of efficacy and safety data from a phase II study in foreign RA patients (A3921025) was used to support the selection of dose. ACR response rates for efficacy and anemia incidence for safety were chosen as the key endpoints for dose selection and the target effect consisted of placebo adjusted response rates of at least 20% for ACR20, 20% for ACR50, and 15% for ACR70 at Week 12 for efficacy and <5% placebo adjusted incidence rate of severe or life-threatening anemia (>2 g/dL decrease in hemoglobin from baseline or an absolute hemoglobin level of <8 g/dL) through 24 weeks for safety. Furthermore, doses for phase III confirmatory studies were selected based on approximately 50% probability of achieving the target effects (PTE) for the above 4 endpoints. PTEs for the 4 endpoints for tofacitinib 1 to 15 mg were as shown in Figure 2, and the 5 mg and 10 mg doses, which approximately met the target effect criteria, were thus selected for further evaluation in phase III confirmatory studies.

In the Japanese phase II study in Japanese RA patients (A3921040), even tofacitinib 3 mg showed similar efficacy to tofacitinib 5 mg based on the primary endpoint of ACR20 response rate, whereas a more rigorous endpoint of ACR70 response rate and a measure of clinical remission, the rate of DAS28-4 (ESR) <2.6 were 13.2% and 2.0%, respectively, in the tofacitinib 3 mg group, which were lower than 26.9% and 16.0%,

7.5-25 mg/week.

respectively, in the tofacitinib 5 mg group. Regarding safety, severe anemia, which was used as a criterion for dose selection for foreign confirmatory studies, was not reported in the Japanese phase II study (A3921040). Although the incidences of adverse events were 43.4% (23 of 53 subjects) in the tofacitinib 3 mg group and 55.8% (29 of 52 subjects) in the tofacitinib 5 mg group and there was a trend towards a dose-dependent increase, the incidences of serious adverse events were 5.7% (3 of 53 subjects) in the tofacitinib 3 mg group and 3.8% (2 of 52 subjects) in the tofacitinib 5 mg group and the incidences of severe adverse events were 3.8% (2 of 53 subjects) in the tofacitinib 3 mg group and 1.9% (1 of 52 subjects) in the tofacitinib 5 mg group and there were no major differences in safety profile between the two doses. Based on the above, the 5 mg and 10 mg doses selected for evaluation in foreign phase III confirmatory studies were appropriate also for Japanese RA patients.

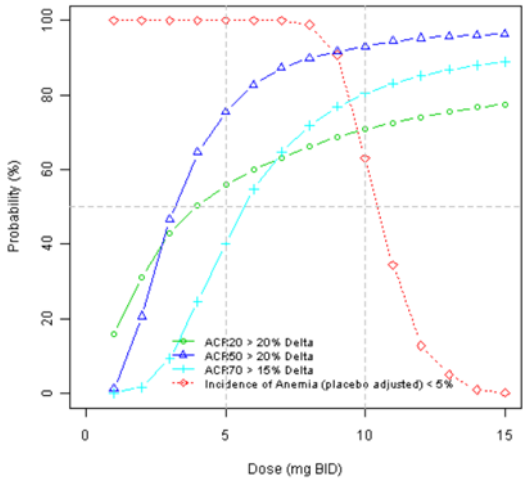


Figure 2. Probability of achieving target effects for efficacy (ACR20, ACR50, and ACR70 response rates) and safety (incidence of anemia) endpoints based on dose-response modeling of A3921025 data

PMDA concluded as follows:

When ACR20 response rates, which was chosen as the primary endpoint for a Japanese phase II study (A3921040) (a bridging study) and a foreign phase II study (A3921035) (a study to be bridged), were compared, the difference between tofacitinib and placebo was greater in Japanese RA patients compared with foreign RA patients at both dose levels. However, with other anti-RA medications, a trend towards a higher ACR response rate in Japanese RA patients than in foreign RA patients has also been observed . In addition, the dose response relationship was largely similar in the two studies. Therefore, it is possible to extrapolate foreign clinical data on the effects of tofacitinib on signs and symptoms of RA such as joint pain to evaluate the efficacy of tofacitinib in Japanese RA patients. Although the Japanese phase II study (A3921040) suggested that even 3 mg of tofacitinib can provide a certain level of efficacy in Japanese patients, the applicant's conclusion that the efficacy of tofacitinib 3 mg is not adequate from a clinical point of view based on its effects on more clinically significant criteria, e.g. ACR70 response rate and the rate of DAS28-4 (ESR) <2.6, is also understood. Therefore, it is acceptable to evaluate the efficacy of tofacitinib in reducing signs and symptoms of RA such as joint pain and the optimum dose in Japanese RA patients based on the data from foreign phase III confirmatory studies at doses of 5 mg and 10 mg.

The applicant explained the effects of tofacitinib in reducing signs and symptoms of RA such as joint pain, including the efficacy at each dose level, as follows:

The effects of tofacitinib in reducing signs and symptoms of RA such as joint pain in a foreign phase III monotherapy study (A3921045), a background MTX global phase III study (A3921044), background MTX foreign phase III studies (A3921032, A3921064), and a background DMARD foreign phase III study (A3921046) were as shown in Table 47. Pairwise comparisons of the results of the primary endpoint of ACR20 response rate yielded statistically significant differences between tofacitinib 5 mg and placebo and between tofacitinib 10 mg and placebo and the efficacy of tofacitinib was confirmed. Concerning the efficacy of 5 mg and 10 mg of tofacitinib, the primary endpoint of ACR20 response rate was almost comparable while ACR70 response rate and the rate of DAS28-4 (ESR) <2.6 were higher in the 10 mg group than in the 5 mg group regardless of whether tofacitinib was administered as a monotherapy or in combination with DMARDs including MTX. Thus, the 10 mg dose of tofacitinib is needed to achieve a greater improvement in clinical symptoms.

Table 47. Comparison of the effects in reducing signs and symptoms of RA such as joint pain between tofacitinib 5 mg and 10 mg (Phase III studies, FAS, NRI)

Endpoint	Treatment group	A3921032[a)]	A3921044[b)]	A3921046[b)]	A3921064[b)]	A3921045[a)]
		Background MTX	Background MTX	Background DMARD	Background MTX	Monotherapy
ACR20 response rate	Placebo	24.43 (32/131)	25.32 (39/154)	31.21 (49/157)	28.30 (30/106)	26.67 (32/120)
	Tofacitinib 5 mg	41.67 (55/132) 17.23 [6.06, 28.41] *P* = 0.0024	51.46 (159/309) 26.13 [17.28, 34.97] *P* < 0.0001	52.73 (164/311) 21.52 [12.39, 30.65] *P* < 0.0001	51.53 (101/196) 23.22 [12.16, 34.29] *P* < 0.0001	59.75 (144/241) 33.08 [23.04, 43.13] *P* < 0.0001
	Tofacitinib 10 mg	48.12 (64./133) 23.69 [12.45, 34.92] *P* < 0.0001	61.81 (191/309) 36.48 [27.73, 45.23] *P* < 0.0001	58.25 (180/309) 27.04 [17.94, 36.13] *P* < 0.0001	52.55 (103/196) 24.24 [13.18, 35.31] *P* < 0.0001	65.70 (159/242) 39.04 [29.12, 48.95] *P* < 0.0001
ACR50 response rate	Placebo	8.40 (11/131)	8.44 (13/154)	12.74 (20/157)	12.26 (13/106)	12.50 (15/120)
	Tofacitinib 5 mg	26.52 (35/132)	32.36 (100/309)	33.76 (105/311)	36.73 (72/196)	31.12 (75/241)
	Tofacitinib 10 mg	27.82 (37/133)	43.69 (135/309)	36.57 (113/309)	34.69 (68/196)	36.78 (89/242)
ACR70 response rate	Placebo	1.53 (2/131)	1.30 (2/154)	3.18 (5/157)	1.89 (2/106)	5.83 (7/120)
	Tofacitinib 5 mg	13.64 (18/132)	14.56 (45/309)	13.18 (41/311)	19.90 (39/196)	15.35 (37/241)
	Tofacitinib 10 mg	10.53 (14/133)	22.33 (69/309)	16.18 (50/309)	21.94 (43/196)	20.25 (49/242)
DAS28-4 (ESR) <2.6	Placebo	1.67 (2/120)	1.55 (2/129)	2.70 (4/148)	1.09 (1/92)	4.39 (5/114)
	Tofacitinib 5 mg	6.72 (8/119)	7.17 (19/265)	9.13 (24/263)	6.21 (11/177)	5.60 (13/232)
	Tofacitinib 10 mg	8.80 (11/125)	15.95 (41/257)	13.33 (36/270)	12.50 (22/176)	8.73 (20/229)

% (n) a) At Month 3, b) At Month 6
Treatment difference [95% CI] and *P*-value are indicated for ACR20 response rate. *P*-values were calculated using a normal approximation.

Foreign phase III studies (A3921032, A3921045, A3921046, A3921064) and a global phase III study (A3921044) had multiple primary endpoints [see "4.(iii).A *Summary of the submitted data*"] and it was necessary to adjust for multiplicity from pairwise comparisons for placebo and tofacitinib 5 mg and 10 mg and the multiple endpoints. The applicant explained the multiplicity adjustment procedure as follows:

In the foreign phase III studies (A3921032, A3921045, A3921046, A3921064) and the global phase III study (A3921044), a sequential gatekeeping or step-down testing procedure was planned to adjust for multiplicity from a total of 6 pairwise comparisons (for 3 primary endpoints, two dose levels of tofacitinib and placebo) or from a total of 8 pairwise comparisons (for 4 primary endpoints, two dose levels of tofacitinib and placebo). All pairwise comparisons were performed at a two-sided significance level of 5%. A pairwise comparison of tofacitinib 10 mg and placebo for a given endpoint was to be performed only if tofacitinib 10 mg at the endpoint of the higher level was statistically significant. A pairwise comparison of tofacitinib 5 mg and placebo for a given endpoint was to be performed only if both tofacitinib 10 mg at the endpoint at the same level are

statistically significant, and tofacitinib 5 mg at the endpoint of the higher level were statistically significant. In the sequential testing procedure, treatment difference in the first endpoint in the sequence, i.e. ACR20 response rate, between placebo and tofacitinib 10 mg was tested first, and at the second and subsequent steps, two sets of comparisons were tested simultaneously at a two-sided significance level of 5%. Thus, this method did not strongly control the type I error rate at the nominal level or below. However, at least, the type I error rate was controlled at the nominal level or below across different endpoints within each tofacitinib dose group, and different doses of tofacitinib vs. placebo within each endpoint. Also, as to the risk of multiplicity of the tests within each step, if the comparison between tofacitinib 10 mg and placebo was significant at previous steps, the situation where the null hypothesis at a given step was true for the tofacitinib 5 mg group was very unlikely. Therefore, the multiplicity adjustment procedure was appropriate.

PMDA's view on the effects of tofacitinib in reducing signs and symptoms of RA such as joint pain is as follows:
With respect to the analysis plans for foreign phase III studies (A3921032, A3921045, A3921046, A3921064) and a global phase III study (A3921044), a more conservative multiplicity adjustment procedure should have been considered (e.g. split the significance level within each step and test each comparison at the two-sided 2.5% significance level). Meanwhile, ACR20 response rate, an important measure of improvement in signs and symptoms of RA such as joint pain, was chosen as the primary endpoint for both monotherapy and background DMARD (including MTX) clinical studies, which consistently demonstrated clinically significant treatment differences between tofacitinib 5 or 10 mg and placebo of 17.23% to 39.04%. Thus, it is possible to conclude based on these results that both tofacitinib 5 mg and 10 mg have been shown to reduce signs and symptoms of RA such as joint pain in Japanese RA patients who have had an inadequate response to existing therapies. Concerning the efficacy of 5 mg and 10 mg of tofacitinib, ACR70 response rate and the rate of DAS 28-4 (ESR) <2.6 tended to be higher with tofacitinib 10 mg than with tofacitinib 5 mg and it is understood that the 10 mg dose may be more useful for some patients, but the optimum dose of tofacitinib for Japanese RA patients will be determined, taking also account of the safety profiles of the two doses [see "4.(iii).B.(3) Dosage and administration"].

4.(iii).B.(1).2) Inhibition of structural damage to joints

The applicant explained the effect of tofacitinib in preventing the progression of joint damage as follows:
A global phase III study (A3921044) enrolled approximately 15% Japanese RA patients and the primary endpoints of ACR20 response rate at Month 6, the change from baseline in mTSS at Month 6, the rate of DAS28-4 (ESR) <2.6 at Month 6, and the change from baseline in HAQ-DI at Month 3 showed a consistent trend towards improvement in the Japanese subpopulation, as in the overall population [see "4.(iii).A *Summary of the submitted data*"]. Therefore, it was concluded that the effect of tofacitinib in preventing the progression of joint damage in Japanese RA patients can be assessed based on the data from this study.

In the global phase III study (A3921044), a pairwise comparison of the results of the primary endpoint of the change from baseline in mTSS at Month 6 yielded a statistically significance difference between tofacitinib 10 mg and placebo (P = 0.0376, ANCOVA model with treatment, site, and baseline value as explanatory variables). On the other hand, pairwise comparison showed no statistically significant difference between

tofacitinib 5 mg and placebo (P = 0.0792, ANCOVA model with treatment, site, and baseline value as explanatory variables). However, the proportions of subjects with no joint damage progression at Month 6 (defined as ≤0.5 unit increase from baseline in mTSS) in the tofacitinib 5 mg and 10 mg groups were similar, which were both statistically significantly higher compared with that in the placebo group, as shown in Table 48. Moreover, the cumulative distribution plots of mTSS changes from baseline to Month 6 were as illustrated in Figure 4. Given that the plots for the tofacitinib 5 mg and 10 mg groups were similar, like tofacitinib 10 mg, tofacitinib 5 mg is also expected to prevent the progression of joint damage.

Pairwise comparison showed no statistically significant difference in the change from baseline in mTSS between tofacitinib 5 mg and placebo, which is considered attributed to a small change from baseline in mTSS at Month 6 (0.47) in the placebo group in this study. Also, according to the recent literature assessing change from baseline in mTSS with other anti-RA drugs, the change in mTSS from baseline to 1 year in the placebo (MTX) group was 1.13 in a study of tocilizumab (Kremer JM, et al. *Arthritis Rheum.* 2011;63:609-621) and the change in mTSS from baseline to Week 24 and the change in mTSS from baseline to 1 year in the placebo (MTX) group were 0.55 and 1.10, respectively, in studies of golimumab (Emery P, et al. *Arthritis Rheum.* 2011;63:1200-1210). Due to advances in the treatment of RA for the prevention of the progression of joint damage, the rate of joint damage progression has been slowing down gradually, resulting in a small change in mTSS from baseline in the placebo group.

Table 48. Proportion of subjects with no joint damage progression[a)] at Month 6
(pairwise comparison vs. placebo, Study A3901044, FAS, LEP)

	Overall population			Japanese subpopulation		
	Tofacitinib 5 mg	Tofacitinib 10 mg	Placebo	Tofacitinib 5 mg	Tofacitinib 10 mg	Placebo
	88.81 (246/277)	86.90 (252/290)	77.70 (108/139)	86.36 (38/44)	75.00 (33/44)	59.09 (13/22)
P-value	P = 0.0055	P = 0.0230	-	P = 0.0196	P = 0.1976	-

n (%), *P*-values were calculated using a normal approximation.
a) ≤0.5 unit increase from baseline in mTSS
b) ANCOVA model with treatment, site, and baseline value as explanatory variables

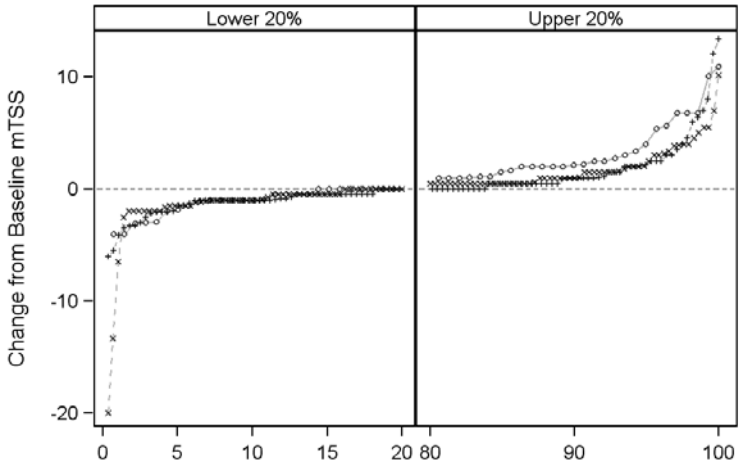


Figure 4. Cumulative distribution plots of mTSS changes from baseline to Month 6 (FAS)
＋: Tofacitinib 5 mg group, ×: Tofacitinib 10 mg group, ○: Placebo group

In the global phase III study (A3921044), as shown in Table 49, the proportion of subjects with no change in joint damage from baseline to Month 6 was high, about 60% in all treatment groups and the treatment difference between each of the tofacitinib groups and placebo group for the change from baseline in mTSS

was smaller compared to what was assumed when planning the study (a treatment difference of 0.8), and the small apparent treatment effect size was susceptible to change depending on analytical approach and extreme observations. Thus, PMDA requested the applicant to check the results of a pre-specified sensitivity analysis using ANCOVA with ranked data in order to assess the robustness of the results and conduct additional analyses of the following endpoints, which are considered useful from the standpoint of clinical interpretation: "the proportion of subjects with no joint structural damage progression" (defined as a change from baseline in mTSS ≤0 or ≤0.5) and "the proportion of subjects who experienced some degree of joint damage progression" (defined as a change from baseline in mTSS ≥ SDD, ≥ 3, or ≥ 4). As a result, as shown in Table 50 and Table 51, most of these analysis results were inconsistent with the findings from the primary analysis and tofacitinib 10 mg tended to be inferior to tofacitinib 5 mg. Thus, the data on the effect of tofacitinib in preventing joint damage progression were not consistent with respect to dose.

Table 49. Joint damage progression at Month 6 with or without linear extrapolation (A3921044, FAS)

	Placebo	Tofacitinib 5 mg	Tofacitinib 10 mg
Joint damage progression			
Improved (change in mTSS <0)	14.04 (8/57) 13.67 (19/139)	18.87 (50/265) 18.05 (50/277)	15.16 (42/277) 15.86 (46/290)
No change (change in mTSS = 0)	56.14 (32/57) 60.43 (84/139)	64.15 (170/265) 65.70 (182/277)	62.09 (172/277) 63.10 (183/290)
Worsened (change in mTSS >0)	29.82 (17/57) 25.90 (36/139)	16.98 (45/265) 16.25 (45/277)	22.74 (63/277) 21.03 (61/290)
Change from baseline in mTSS			
Mean (SD)	0.18 (1.30) 0.49 (2.02)	0.09 (1.20) 0.13 (1.72)	0.05 (1.71) 0.08 (1.95)
Min., Max.	-4.00, 4.00 -4.00, 10.88	-5.50, 8.00 -6.03, 13.37	-20.00, 7.00 -20.00, 10.16

% (n) Lower row: Linear extrapolation method for missing data imputation

Table 50. Results of analysis on changes from baseline in mTSS at Month 6 based on the ranks (A3921044, FAS, LEP)

	Overall population			Japanese subpopulation		
	n	Mean rank	Treatment difference, *P*-value[a)]	n	Mean rank	Treatment difference, *P*-value[a)]
Tofacitinib 5 mg	277	334.34	-41.26, *P* = 0.0237	44	324.40	-111.2, *P* = 0.0310
Tofacitinib 10 mg	290	352.33	-23.27, *P* = 0.1978	44	391.34	-44.29, *P* = 0.3861
Placebo	139	375.60	-	22	435.63	-

ANCOVA model with treatment, site, and baseline mTSS (ranked data) as explanatory variables

Table 51. Proportion of subjects with change from baseline in mTSS at Month 6 of ≤0, ≤0.5, ≥ SDD, ≥3, or ≥4 (A3921044, FAS, LEP)

	Overall population		Japanese subpopulation	
	% (n)	Treatment difference [95% CI], *P*-value	% (n)	Treatment difference [95% CI], *P*-value
Change in mTSS ≤0				
Tofacitinib 5 mg	83.75 (232/277)	9.65 [1.17, 18.13], *P* = 0.0257	81.82 (36/44)	22.73 [-0.77, 46.22], *P* = 0.0580
Tofacitinib 10 mg	78.97 (229/290)	4.86 [-3.80, 13.53], *P* = 0.2710	70.45 (31/44)	11.36 [-13.21, 35.94], *P* = 0.3647
Placebo	74.10 (103/139)	-	59.09 (13/22)	-
Change in mTSS ≤0.5 (Secondary endpoint)				
Tofacitinib 5 mg	88.81 (246/277)	11.11 [3.25, 18.96], *P* = 0.0055	86.36 (38/44)	27.27 [4.36, 50.18], *P* = 0.0196
Tofacitinib 10 mg	86.90 (252/290)	9.19 [1.26, 17.13], *P* = 0.0230	75.00 (33/44)	15.91 [-8.29, 40.11], *P* = 0.1976
Placebo	77.70 (108/139)	-	59.09 (13/22)	-
Change in mTSS ≥ SDD[a)]				
Tofacitinib 5 mg	7.94 (22/277)	-7.89 [-14.74, -1.03], *P* = 0.0241	6.82 (3/44)	-25.00 [-45.84, -4.16], *P* = 0.0187
Tofacitinib 10 mg	9.66 (28/290)	-6.17 [-13.13, 0.78], *P* = 0.0820	15.91 (7/44)	-15.91 [-38.17, 6.35], *P* = 0.1613
Placebo	15.83 (22/139)	-	31.82 (7/22)	-
Change in mTSS ≥3				
Tofacitinib 5 mg	3.97 (11/277)	-3.22 [-8.09, 1.64], *P* = 0.1947	2.27 (1/44)	-15.91 [-32.62, 0.80], *P* = 0.0620
Tofacitinib 10 mg	4.83 (14/290)	-2.36 [-7.32, 2.58], *P* = 0.3490	11.36 (5/44)	-6.82 [-25.46, 11.83], *P* = 0.4736
Placebo	7.19 (10/139)	-	18.18 (4/22)	-
Change in mTSS ≥4				
Tofacitinib 5 mg	2.89 (8/277)	-2.86 [-7.21, 1.47], *P* = 0.1958	0.00 (0/44)	-18.18 [-34.30, -2.06], *P* = 0.0270
Tofacitinib 10 mg	2.76 (8/290)	-2.99 [-7.30, 1.30], *P* = 0.1725	4.55 (2/44)	-13.64 [-30.89, 3.62], *P* = 0.1213
Placebo	5.76 (8/139)	-	18.18 (4/22)	-

a) SDD was 1.38 at Month 6.
P-values were calculated using a normal approximation.

Furthermore, PMDA checked the distribution of changes from baseline in mTSS. As illustrated in Figure 5, 1 subject had a change from baseline in mTSS at Month 6 of −20.0 units and 1 subject had a change of −13.4 units in the tofacitinib 10 mg group, which were clinically unlikely degrees of change. Thus, PMDA requested the applicant to repeat the primary analysis after excluding these observations. As a result, as shown in Table 52, the results from this primary analysis showed no statistically significant difference between tofacitinib 10 mg and placebo, suggesting that the significant findings were driven by the data from these 2 subjects.

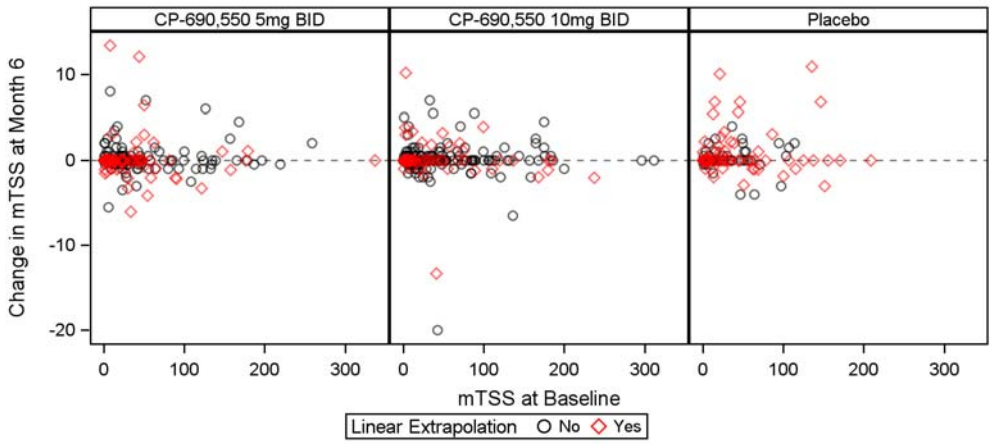


Figure 5. Scatter plots of changes from baseline in mTSS at Month 6 (A3921044, FAS, LEP)

Table 52. Results of primary analysis excluding outlying subjects: Change from baseline in mTSS at Month 6 (A3921044, FAS, LEP)

		n	Baseline	Change (range)	LS mean[a)]	Treatment difference [95% CI][a)], *P*-value[a)]
All subjects	Tofacitinib 5 mg	277	31.11 ± 47.71	0.13 ± 1.72 (-6.03, 13.37)	0.12	-0.34 [-0.73, 0.04], *P* = 0.0792
	Tofacitinib 10 mg	290	37.30 ± 54.10	0.08 ± 1.95 (-20.00, 10.16)	0.06	-0.40 [-0.79, -0.02], *P* = 0.0376
	Placebo	139	32.60 ± 41.80	0.49 ± 2.02 (-4.00, 10.88)	0.47	-
Excluding 1 subject	Tofacitinib 5 mg	277	31.11 ± 47.71	0.13 ± 1.72 (-6.03, 13.37)	0.11	-0.34 [-0.69, 0.01], *P* = 0.0564
	Tofacitinib 10 mg	289	37.24 ± 54.19	0.15 ± 1.56 (-13.35, 10.16)	0.12	-0.33 [-0.68, 0.02], p= 0.0614
	Placebo	139	32.60 ± 41.80	0.49 ± 2.02 (-4.00, 10.88)	0.45	-
Excluding 2 subjects	Tofacitinib 5 mg	277	31.11 ± 47.71	0.13 ± 1.72 (-6.03, 13.37)	0.11	-0.34 [-0.68, -0.01], *P* = 0.0466
	Tofacitinib 10 mg	288	37.23 ± 54.28	0.20 ± 1.34 (-6.50, 10.16)	0.17	-0.29 [-0.62, 0.05], *P* = 0.0933
	Placebo	139	32.60 ± 41.80	0.49 ± 2.02 (-4.00, 10.88)	0.45	-

No. of subjects included in analysis, Mean ± SD
a) ANCOVA model with treatment, site, and baseline value as explanatory variables

Based on the results of these analyses, PMDA's view on the effect of tofacitinib in preventing joint structural damage is as follows:

The applicant explained that, based on the data from a global phase III study assessing the effect of tofacitinib in preventing joint structural damage (A3921044), the primary analysis of change from baseline in mTSS demonstrated the superiority of tofacitinib 10 mg over placebo and although the superiority of tofacitinib 5 mg over placebo was not demonstrated, as tofacitinib 5 mg produced similar results as tofacitinib 10 mg, the both doses of tofacitinib are expected to prevent joint structural damage.

However, taking account of the results of an analysis on changes from baseline in mTSS based on the ranks, which was pre-specified as a sensitivity analysis, and additional analyses including that of the secondary endpoint (the proportion of subjects with no joint structural damage progression, the proportion of subjects who experienced some degree of joint damage progression, an analysis after excluding observations with clinically unlikely degrees of change in mTSS at Month 6), it is difficult to conclude that the results of this study demonstrated robust efficacy of tofacitinib in preventing joint damage progression. Pairwise comparison showed a statistically significant difference between tofacitinib 10 mg and placebo, which was considered to be driven by subjects with clinically unlikely degrees of change. Given that about 60% of subjects in the placebo group had no change in joint structural damage in this study, it seemed that great progression of joint structural damage was unlikely to occur in this study population, which also affected the assessment.

Based on the above, although this study suggested the effectiveness of tofacitinib at both 5 mg and 10 mg in preventing joint structural damage, it is difficult to conclude based only on these results that the efficacy of tofacitinib in preventing joint structural damage was demonstrated.

The above conclusions on the efficacy of tofacitinib by PMDA will be discussed at the Expert Discussion.

4.(iii).B.(2) Safety

The applicant explained an overview of adverse events in Japanese and foreign clinical studies in RA patients as follows. In the following explanations, the data from Japanese and foreign clinical studies in RA patients (data cut-off date of March 29, 2011) (a total of 4816 unique subjects who received at least one dose of tofacitinib)[41] and the pooled data from phase III studies (0-3 months, allowing for comparison with placebo) and the pooled data from long-term extension studies (data cut-off date of March 29, 2011) for parallel-group comparison are primarily used.

Table 53 shows an overview of adverse events based on the pooled data from the phase III studies and the pooled data from the long-term extension studies.

Table 53. Overview of adverse events (Phase III studies[a)] [0-3 months], Long-term extension studies[b)])

	Phase III studies				Long-term extension studies	
	Tofacitinib 5 mg (n = 1216)	Tofacitinib 10 mg (n = 1214)	Placebo (n = 681)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1321)	Tofacitinib 10 mg (n = 1906)
Subjects with adverse events	624 (51.3)	653 (53.8)	363 (53.3)	105 (51.5)	1047 (79.3)	1088 (57.1)
Subjects with serious adverse event	36 (3.0)	35 (2.9)	25 (3.7)	5 (2.5)	209 (15.8)	114 (6.0)
Subjects with severe adverse event	49 (4.0)	39 (3.2)	28 (4.1)	6 (2.9)	153 (11.6)	98 (5.1)
Subjects discontinued due to adverse event	52 (4.3)	49 (4.0)	22 (3.2)	10 (4.9)	148 (11.2)	75 (3.9)
Subjects with treatment interrupted due to adverse event[c)]	103 (8.5)	99 (8.2)	38 (5.6)	15 (7.4)	353 (26.7)	259 (13.6)
Subjects with adverse event for which a causal relationship to study drug could not be denied	372 (30.6)	393 (32.4)	169 (24.8)	54 (26.5)	748 (56.6)	617 (32.4)

n (%)
a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041
c) Including subjects with dose reduced for long-term extension studies

According to the pooled data from the phase III studies, adverse events commonly reported with tofacitinib (≥3%) in 0 to 3 months included upper respiratory tract infection (tofacitinib 5 mg group, 4.4% [53 of 1216 subjects]; tofacitinib 10 mg group, 3.9% [47 of 1214 subjects]; adalimumab group, 3.4% [7 of 204 subjects]; placebo group, 3.4% [23 of 681 subjects]), headache (tofacitinib 5 mg group, 4.4% [54 of 1216 subjects]; tofacitinib 10 mg group, 3.2% [39 of 1214 subjects]; adalimumab group, 2.5% [5 of 204 subjects]; placebo group, 2.2% [15 of 681 subjects]), nasopharyngitis (tofacitinib 5 mg group, 3.9% [47 of 1216 subjects]; tofacitinib 10 mg group, 2.9% [35 of 1214 subjects]; adalimumab group, 3.4% [7 of 204 subjects]; placebo group, 2.8% [19 of 681 subjects]), and diarrhoea (tofacitinib 5 mg group, 3.7% [45 of 1216 subjects];

[41] Phase II studies (A3921019, A3921025, A3921035, A3921039, A3921040; 1369 subjects who received at least one dose of tofacitinib), phase III studies (A3921032, A3921044, A3921045, A3921046, A3921064; 3030 subjects who received at least one dose of tofacitinib), and long-term extension studies (A3921024, A3921041; 3227 subjects who received at least one dose of tofacitinib)

tofacitinib 10 mg group, 2.8% [34 of 1214 subjects]; adalimumab group, 1.0% [2 of 204 subjects]; placebo group, 2.3% [16 of 681 subjects]). The nature and incidence of adverse events reported in phase III background DMARD studies and in a phase III monotherapy study were similar to those in the overall phase III studies. According to the pooled data from the long-term extension studies, adverse events commonly reported with tofacitinib (≥3%) included nasopharyngitis (10.0%), upper respiratory tract infection (7.3%), urinary tract infection (4.6%), bronchitis (4.5%), hypertension (4.2%), herpes zoster (4.1%), headache (3.7%), influenza (3.3%), and back pain (3.3%).

In the phase III background DMARD studies (A3921032, A3921044, A3921046, A3921064), the incidences of serious adverse events in 0 to 3 months were 3.8% in the tofacitinib 5 mg group, 2.9% in the tofacitinib 10 mg group, 3.4% in the placebo group, and 2.5% in the adalimumab group. Serious adverse events commonly reported with tofacitinib (≥3%) were those classified as "infections and infestations" and the most commonly reported serious adverse events were pneumonia and cellulitis. In the phase III monotherapy study (A3921045), the incidences of serious adverse events in 0 to 3 months were 0.4% in the tofacitinib 5 mg group, 2.0% in the tofacitinib 10 mg group, and 4.1% in the placebo group and the incidences of serious adverse events in the tofacitinib 5 mg and 10 mg groups tended to be lower in the monotherapy study compared with the background DMARD studies. According to the pooled data from the long-term extension studies, serious adverse events commonly reported with tofacitinib (≥6 subjects) included pneumonia (23 subjects), osteoarthritis (15 subjects), herpes zoster (8 subjects), urinary tract infection (8 subjects), cholelithiasis (7 subjects), fall (7 subjects), tendon rupture (7 subjects), cellulitis (6 subjects), diverticulitis (6 subjects), and deep vein thrombosis (6 subjects).

In the phase III background DMARD studies, the incidences of adverse events leading to discontinuation in 0 to 3 months were 5.1% in the tofacitinib 5 mg group, 4.4% in the tofacitinib 10 mg group, 3.0% in the placebo group, and 4.9% in the adalimumab group and adverse events leading to discontinuation in the tofacitinib 5 mg and 10 mg groups were mainly those classified as "infections and infestations." In the phase III monotherapy study, the incidences of adverse events leading to discontinuation in 0 to 3 months were 0.8% in the tofacitinib 5 mg group, 2.4% in the tofacitinib 10 mg group, and 4.1% in the placebo group and adverse events leading to discontinuation were mainly those classified as "gastrointestinal disorders" in both tofacitinib and placebo groups. According to the pooled data from the long-term extension studies, adverse events leading to discontinuation in subjects treated with tofacitinib were mainly those classified as "infections and infestations" and "neoplasms benign, malignant and unspecified (incl cysts and polyps)" and the main events were pneumonia, herpes zoster, and ALT increased.

Of the 4816 unique subjects who received at least one dose of tofacitinib in Japanese and foreign clinical studies in RA patients, 34 deaths were reported. Of which, 21 deaths occurred within 30 days of the last dose. The most common causes of death were infections (especially, pneumonia) and malignancies. According to the pooled data from the phase III studies and the pooled data from the long-term extension studies, the exposure-adjusted incidence rates of deaths were as shown in Table 54.

Table 54. Exposure-adjusted incidence rate of deaths
(Phase III studies[a)] [0-3 months], Long-term extension studies[b)])

	Phase III studies				Long-term extension studies	
	Tofacitinib 5 mg (n = 1216)	Tofacitinib 10 mg (n = 1214)	Placebo (n = 681)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1321)	Tofacitinib 10 mg (n = 1906)
n (%) Lower row: Japanese deaths	7 (0.58) 2	4 (0.33) 0	1 (0.15) 0	1 (0.49) 0	17 (1.29) 2	3 (0.16) 0
Incidence rate of deaths (/100 patient-years) [95% CI]	0.78 [0.37, 1.62]	0.44 [0.17, 1.17]	0.49 [0.07, 3.51]	0.56 [0.08, 3.97]	0.76 [0.47, 1.22]	0.34 [0.11, 1.06]
Total exposure (patient-years)	903.64	910.37	202.55	178.94	2236.41	881.91

a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041

Concerning an overview of adverse events in Japanese and foreign RA patients, the results of comparison based on a bridging study (A3921040), a study to be bridged (A3921035), and a global study (A3921044) were as follows:

According to the data from the bridging study (A3921040) and the study to be bridged (A3921035), the incidence of adverse events tended to increase in a dose-dependent manner in both the Japanese and foreign studies (bridging study, 55.8% in the tofacitinib 5 mg group, 60.4% in the tofacitinib 10 mg group, 51.9% in the tofacitinib 15 mg group, 44.2% in the placebo group; study to be bridged, 49.0% in the tofacitinib 5 mg group, 50.8% in the tofacitinib 10 mg group, 52.6% in the tofacitinib 15 mg group, 40.7% in the placebo group). The nature of adverse events was similar between the Japanese and foreign studies and there were also no major differences in the incidence of serious adverse events (0%-5.7% in the Japanese study, 0%-2.0% in the foreign study) or adverse events leading to discontinuation (0%-5.7% in the Japanese study, 0%-3.9% in the foreign study) etc.

According to the data from the global study (A3921044), the incidences of adverse events, adverse events leading to discontinuation, and adverse events leading to interruption during 0 to 3 months tended to be higher in the Japanese subpopulation than in the overall population (Table 55). Most of the adverse events leading to interruption were those classified as “infections and infestations” and the main event was nasopharyngitis. With respect to laboratory changes, liver function tests (ALT and AST) >3 times the upper limit of normal and moderate to severe (500 to <1500/mm^3) neutropenia tended to occur more frequently in the tofacitinib 10 mg group in the Japanese subpopulation compared with the tofacitinib 5 mg group in the Japanese subpopulation and the overall population, whereas the trend of occurrence of adverse events was largely similar between the overall population and the Japanese subpopulation.

Table 55. Overview of adverse events in global phase III study (A3921044) (0-3 months)

	Overall population			Japanese subpopulation		
	Placebo (n = 160)	Tofacitinib 5 mg (n = 321)	Tofacitinib 10 mg (n = 316)	Placebo (n = 24)	Tofacitinib 5 mg (n = 47)	Tofacitinib 10 mg (n = 47)
Subjects with adverse events	73 (45.6)	157 (48.9)	171 (54.1)	9 (37.5)	25 (53.2)	32 (68.1)
Subjects with serious adverse event	5 (3.1)	12 (3.7)	10 (3.2)	0	2 (4.3)	2 (4.3)
Subjects with severe adverse event	6 (3.8)	16 (5.0)	6 (1.9)	0	1 (2.1)	1 (2.1)
Subjects discontinued due to adverse event	5 (3.1)	15 (4.7)	14 (4.4)	0	2 (4.3)	5 (10.6)
Subjects with treatment interrupted due to adverse event	5 (3.1)	22 (6.9)	29 (9.2)	1 (4.2)	7 (14.9)	10 (21.3)
Subjects with adverse event for which a causal relationship to study drug could not be denied	41 (25.6)	98 (30.5)	105 (33.2)	7 (29.2)	23 (48.9)	28 (59.6)

n (%)

4.(iii).B.(2).1) Adverse events potentially related to tofacitinib

Taking account of the trend of occurrence of adverse events in clinical studies and the pharmacological effects of tofacitinib etc., PMDA conducted a review, focusing on the following events.

4.(iii).B.(2).1).(a) Infections

(1) Serious infections

The applicant explained the occurrence of serious infections as follows:

According to the pooled data from phase III studies and the pooled data from long-term extension studies, the exposure-adjusted incidence rates of serious infections and opportunistic infections were as shown in Table 56 and the incidence rates were higher in the tofacitinib 5 mg and 10 mg groups than in the placebo group or the adalimumab group. According to the pooled data from the long-term extension studies, the incidence rates in the tofacitinib 10 mg group were approximately 2-fold higher than those in the tofacitinib 5 mg group.

Table 56. Exposure-adjusted incidence rates of serious infections and opportunistic infections (Phase III studies[a] [0-12 months], Long-term extension studies[b])

		Phase III studies				Long-term extension studies	
		Tofacitinib 5 mg (n = 1216)	Tofacitinib 10 mg (n = 1214)	Placebo (n = 681)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1321)	Tofacitinib 10 mg (n = 1906)
Serious infections	n (%)	29 (2.4)	27 (2.2)	3 (0.4)	3 (1.5)	50 (3.8)	43 (2.3)
	Incidence rate (/100 patient-years) [95% CI]	3.22 [2.24, 4.63]	2.97 [2.04, 4.33]	1.48 [0.48, 4.59]	1.68 [0.54, 5.21]	2.25 [1.71, 2.97]	4.89 [3.63, 6.60]
Opportunistic infections	n (%)	3 (0.2)	10 (0.8)	0	0	8 (0.6)	5 (0.3)
	Incidence rate (/100 patient-years) [95% CI]	0.33 [0.11, 1.03]	1.10 [0.59, 2.04]	0	0	0.36 [0.18, 0.72]	0.57 [0.24, 1.36]

a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041

The exposure-adjusted incidence rates of serious infections by age group were as shown in Table 57 and the incidence rates tended to be higher in subjects aged ≥65 years compared with subjects aged <65 years.

Table 57. Exposure-adjusted incidence rate of serious infections by age group
(Phase III studies[a] [0-12 months], Long-term extension studies[b])

			Phase III studies				Long-term extension studies	
			Tofacitinib 5 mg	Tofacitinib 10 mg	Placebo	Adalimumab	Tofacitinib 5 mg	Tofacitinib 10 mg
Serious infections	<65 years	n (%)	19/1026 (1.9)	21/1030 (2.0)	3/580 (0.5)	1/174 (0.6)	37/1107 (3.3)	26/1578 (1.7)
		Incidence rate (/100 patient-years) [95% CI]	2.47 [1.57, 3.87]	2.69 [1.75, 4.12]	1.73 [0.56, 5.36]	0.65 [0.09, 4.63]	2.00 [1.45, 2.76]	3.50 [2.39, 5.15]
	≥65 years	n (%)	10/190 (5.3)	6/184 (3.3)	0/101 (0)	2/30 (6.7)	13/214 (6.1)	17/327 (5.2)
		Incidence rate (/100 patient-years) [95% CI]	7.63 [4.10, 14.17]	4.71 [2.12, 10.49]	0	7.87 [1.97, 31.47]	3.49 [2.03, 6.02]	12.39 [7.70, 19.93]

a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041

Furthermore, based on the pooled data from phase II, phase III, and long-term extension studies, the occurrence of serious infections by race was examined. As a result, as shown in Table 58, the exposure-adjusted incidence rate tended to be slightly higher in the Japanese population and in the Asian population including Japanese subjects, which were similar to the incidence rate of serious infections with DMARDs (1.4-4.1/100 patient-years) or anti-TNF agents (2.6-18.1/100 patient-years) based on published data.[42] Of the serious infections, serious opportunistic infections (tuberculosis, pneumocystis pneumonia, herpes zoster, non-tuberculous mycobacteriosis, cytomegalovirus infection, cryptococcal infection, etc.) occurred in 14 subjects in the Japanese population, 20 subjects in the Asian population including Japanese subjects, and 14 subjects in the non-Asian foreign population.

Table 58. Exposure-adjusted incidence rate of serious infections by race
(Phase II, Phase III, and long-term extension studies[a])

	Japanese population	Asian population (including Japanese subjects)	Non-Asian foreign population
n	556	1062	3727
Subjects with serious infections (%)	30 (5.4)	52 (4.9)	115 (3.1)
Incidence rate (/100 patient-years) [95% CI]	4.26 [2.98, 6.09]	4.29 [3.27, 5.63]	2.61 [2.17, 3.13]

a) A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044, A3921045, A3921046, A3921064, A3921109

The following safety measures against serious infections will be taken:

· It will be stated in the warnings section of the package insert that fatal infections have been reported, etc.

· Tofacitinib will be contraindicated or careful administration of tofacitinib will be recommended in patients with risk factors for infections.

· The package insert will caution against coadministration with biologics or potent immunosuppressive drugs (tacrolimus, azathioprine, cyclosporine, mizoribine, etc.) because an increased risk of infections is expected due to added immunosuppression.

PMDA considers as follows:

Although the applicant explained that the exposure-adjusted incidence rate of serious infections with tofacitinib was similar to the incidence rate with DMARDs or anti-TNF agents based on published data, the incidence rate was higher with tofacitinib than with adalimumab (an anti-TNF agent) (the active control in some tofacitinib clinical studies), which should be emphasized. Moreover, given that a trend towards a higher

[42] Kroesen S, et al. *Rheumatology (Oxford).* 2003;42:617-621, Dixon WG, et al. *Arthritis Rheum.* 2006;54:2368-2376, Carmona L, et al. *Ann Rheum Dis.* 2007;66:880-885, Curtis JR, et al. *Arthritis Rheum.* 2007;56:1125-1133, Salliot C, et al. *Rheumatology (Oxford).* 2007;46:327-334, Favalli EG, et al. *Autoimmun Rev.* 2009;8:266-273, Galloway JB, et al. *Rheumatology (Oxford).* 2011;50:124-131, Kievit W, et al. *Rheumatology (Oxford).* 2011;50:196-203.

incidence rate in Japanese and Asian subjects than in other racial groups has been suggested, strict safety measures against serious infections during treatment with tofacitinib need to be taken, as the applicant explained. It should also be noted that the exposure-adjusted incidence rate of serious infections tended to be higher in the tofacitinib 10 mg group (4.89/100 patient-years) than in the tofacitinib 5 mg group (2.25/100 patient-years) in long-term extension studies and there was a trend towards a more notable difference between the doses, especially in the elderly (tofacitinib 5 mg group, 3.49/100 patient-years; tofacitinib 10 mg group, 12.39/100 patient-years). RA patients often have decreased immune function due to the use of immunosuppressive, anti-rheumatic drugs or corticosteroids etc., chronic use of tofacitinib in combination with these drugs is also expected, and furthermore, low-body-weight (e.g. <40 kg) Japanese elderly patients with RA are also common and a higher systemic exposure is expected in these patients. Taking account of these findings etc., the risk of serious infections associated with tofacitinib 10 mg is particularly a serious concern for Japanese RA patients. Thus, the clinical dose of tofacitinib should be determined carefully, taking also account of the occurrence of other adverse events, etc.

(2) Herpes zoster and viral reactivation

The applicant explained the occurrence of herpes zoster as follows:

According to the pooled data from phase III studies and the pooled data from long-term extension studies, the exposure-adjusted incidence rates of herpes zoster and serious herpes zoster were as shown in Table 59 and although the incidence rates of herpes zoster and serious herpes zoster were higher in the tofacitinib 5 mg and 10 mg groups than in the placebo group or the adalimumab group, no dose response relationship was observed and there was no increase in the incidence rate after long-term treatment. According to the pooled data from the phase III studies, the incidence rates in the tofacitinib 5 mg and 10 mg groups were higher in background DMARD studies (A3921032, A3921044, A3921046, A3921064) than in a monotherapy study (A3921045) and while the incidence rate [95% CI] was similar for the tofacitinib 5 mg and 10 mg groups in the background DMARD studies (tofacitinib 5 mg group, 4.93/100 [3.59, 6.77] patient-years; tofacitinib 10 mg group, 4.46/100 [3.20, 6.21] patient-years), the incidence rate in the tofacitinib 10 mg group (2.64/100 [0.85, 8.19] patient-years) was higher than that in the tofacitinib 5 mg group (0.85/100 [0.12, 6.06] patient-years) in the monotherapy study.

Table 59. Exposure-adjusted incidence rates of herpes zoster and serious herpes zoster (Phase III studies[a] [0-12 months], Long-term extension studies[b])

		Phase III studies				Long-term extension studies	
		Tofacitinib 5 mg (n = 1216)	Tofacitinib 10 mg (n = 1214)	Placebo (n = 681)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1321)	Tofacitinib 10 mg (n = 1906)
Herpes zoster	n (%)	39 (3.2)	38 (3.1)	3 (0.4)	5 (2.5)	91 (6.9)	43 (2.3)
	Incidence rate (/100 patient-years) [95% CI]	4.39 [3.21, 6.01]	4.23 [3.08, 5.82]	1.49 [0.48, 4.61]	2.81 [1.17, 6.76]	4.25 [3.46, 5.22]	4.95 [3.67, 6.67]
Serious herpes zoster	n (%)	4 (0.3)	1 (<0.1)	0	0	7 (0.5)	1 (<0.1)
	Incidence rate (/100 patient-years) [95% CI]	0.44 [0.17, 1.18]	0.11 [0.02, 0.78]	0	0	0.31 [0.15, 0.66]	0.11 [0.02, 0.81]

a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041

According to the pooled data from phase II, phase III, and long-term extension studies, the exposure-adjusted incidence rate of herpes zoster by race was as shown in Table 60 and the incidence rate of herpes zoster was higher in Asian subjects compared with other races.

Table 60. Exposure-adjusted incidence rate of herpes zoster by race
(Phase II, Phase III, and long-term extension studies[a])

	Caucasian (n = 2875)	Black (n = 139)	Asian (n = 1326)	Others (n = 442)
Subjects with herpes zoster (%)	114 (4.0)	3 (2.2)	107 (8.1)	15 (3.4)
Incidence rate (/100 patient-years) [95% CI]	3.32 [2.76, 3.99]	2.29 [0.74, 7.10]	7.60 [6.29, 9.19]	2.98 [1.79, 4.94]

a) A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044, A3921045, A3921046, A3921064, A3921109

According to the pooled data from phase II, phase III, and long-term extension studies (4816 subjects who received at least one dose of tofacitinib), 59 Japanese RA patients had herpes zoster. Of whom, 10 patients had serious herpes zoster and all of them recovered except for 1 case of herpes zoster oticus (improved). Also in a global phase III study (A3921044), the incidences of herpes zoster in 0 to 3 months were 2.1% (1 of 47 subjects) in the tofacitinib 5 mg group and 6.4% (3 of 47 subjects) in the tofacitinib 10 mg group in the Japanese subpopulation, which tended to be higher than in the overall population (tofacitinib 5 mg group, 0.9% [3 of 321 subjects]; tofacitinib 10 mg group, 1.6% [5 of 316 subjects]). In a Japanese long-term extension study (A3921041), the incidences of herpes zoster were 10.1% (34 of 338 subjects) in the tofacitinib 5 mg group and 9.1% (6 of 66 subjects) in the tofacitinib 10 mg group and the incidence tended to increase after long-term treatment. Meanwhile, the incidences of serious herpes zoster with long-term treatment with biologics, i.e. infliximab, etanercept, and tocilizumab, in Japanese patients were 4.2%, 0.2%, and 4.9%, respectively (Sakai R, et al. *Arthritis Care Res (Hoboken).* 2012;64:1125-1134, Koike T, et al. *J Rheumatol.* 2009;36:898-906, Nishimoto N, et al. *Ann Rheum Dis.* 2009;68:1580-1504), which were not substantially different from the incidence (1.5%) in the tofacitinib long-term extension study (A3921041).

PMDA asked the applicant to discuss the cause for a higher incidence rate of herpes zoster with tofacitinib than with placebo or adalimumab.

The applicant explained as follows:
Both innate (IFNα/β, etc. play a major role) and adaptive (INFγ and TNF-α, etc. play a major role) immune responses contribute to human defense against the varicella-zoster virus, which causes herpes zoster (Novakova L, et al. *Cell Immunol.* 2011;269:78-81) and tofacitinib inhibits cytokine production by both innate and adaptive immunity via inhibition of JAK/STAT phosphorylation (Ghoreschi K, et al. *J Immunol.* 2011;186:4234-4243). In addition, IFNγ is involved in herpesvirus infections (Bosnjak L, et al. *Viral Immunol.* 2005;18:419-433) and the varicella-zoster virus inhibits IFNγ induced MHC class II expression, facilitating local virus replication and transmission during the initial stage of infection, by inhibiting the expression of STAT1 and JAK2 proteins (Abendroth A, et al. *J Virol.* 2000;74:1900-1907). Therefore, tofacitinib may have increased the incidence rate of herpes zoster by inhibiting JAK/STAT phosphorylation and thus facilitating varicella-zoster virus replication and transmission, in addition to inhibiting the production of cytokines, e.g., TNF-α, IFNα/β, and INFγ, involved in the defense against viral infections,.

PMDA considers as follows:
Herpes zoster is an adverse event as expected from the mode of action of tofacitinib and is considered to represent a characteristic event among infections associated with tofacitinib. The incidence of herpes zoster tended to be higher in Japanese patients compared with foreign patients and among 14 Japanese RA patients

treated with tofacitinib who had serious opportunistic infections, 10 patients had serious herpes zoster. Taking account of these findings, the possiblitity for the development of herpes zoster should be mentioned separately from other infections in the package insert etc. to call attention.

Given that tofacitinib inhibits the production of cytokines, e.g., TNF-α, IFNα/β, and INFγ, involved in the defense against viral infections, the possibility of the reactivation of not only varicella-zoster virus, but also other viruses should be noted as well. As cases of viral reactivation or suspected viral reactivation associated with tofacitinib, 1 case of hepatitis B (HB) in the tofacitinib 10 mg group was reported in a foreign long-term extension study (A3921024) and 1 case of positive HBs antigen in the tofacitinib 5 mg group was reported in a Japanese long-term extension study (A3921041). In addition, 1 case of BK virus encephalitis in the tofacitinib 5 mg group was reported in the foreign long-term extension study (A3921024) and 4 cases of BK virus nephropathy in the tofacitinib 30 mg group and 2 cases of BK viraemia in the tofacitinib 15 mg group were reported in a phase II study in de novo kidney allograft recipients though these doses were higher than the proposed clinical doses of tofacitinib (S. Busque, et al. *Am J Transplant.* 2009;9:1936-1945). Furthermore, as described in "3.(iii) Summary of toxicology studies," in foreign clinical studies of tofacitinib in renal transplant patients, lymphomas occurred in 5 patients who received 15 mg of tofacitinib followed by a reduced dose of 10 mg, in combination with multiple immunosuppressive drugs, and all of these 5 patients were EBV-positive. Therefore, it is necessary to appropriately provide the above information to medical practice and then adequately caution about the possibility of viral reactivation during treatment with tofacitinib. As these viruses have been suggested to be associated with not only infections, but also malignancies, it is also necessary to investigate the relationship between viral reactivation associated with tofacitinib and the development of malignancy via post-marketing surveillance.

(3) Tuberculosis

The applicant explained the occurrence of tuberculosis as follows:

According to the pooled data from phase III studies and the pooled data from long-term extension studies, the exposure-adjusted incidence rates of tuberculosis were as shown in Table 61. According to the pooled data from the phase III studies, tuberculosis occurred only in subjects treated with tofacitinib 10 mg, but there was no increase in the incidence rate after long-term treatment.

Table 61. Exposure-adjusted incidence rate of tuberculosis
(Phase III studies[a)] [0-12 months], Long-term extension studies[b)])

	Phase III studies				Long-term extension studies	
	Tofacitinib 5 mg (n = 1216)	Tofacitinib 10 mg (n = 1214)	Placebo (n = 681)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1321)	Tofacitinib 10 mg (n = 1906)
n (%)	0	6 (0.5)	0	0	1 (<0.1)	1 (<0.1)
Incidence rate (/100 patient-years) [95% CI]	0	0.66 [0.30, 1.47]	0	0	0.05 [0.01, 0.32]	0.11 [0.02, 0.81]

a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041

PMDA asked the applicant to explain the risk of tuberculosis associated with tofacitinib, taking also account of comparison with existing biologics and DMARDs.

The applicant explained as follows:

Although alveolar macrophages play a central role in innate immunity in the initial phase of tuberculosis infection, as innate immunity alone is unable to kill the bacteria sufficiently, it is known that adaptive immune control of the bacteria (cytokines such as IFNγ and TNF-α play a major role) is important (Akagawa K. *Kekkaku.* 2012;87:61-70, Eguchi K. *Respiratory Medicine*. 2008;13:84-91). As tofacitinib not only inhibits IFNγ production through JAK/STAT inhibition, but also blocks the effects of TNF by inhibiting TNF-induced expression of chemokines (IP-10, RANTES, MCP-1) (Rosengren S, et al. *Ann Rheum Dis*. 2012;71:440-447), it is thought that major cytokines involved in the defense against tuberculosis infection are extensively inhibited by tofacitinib.

In the US, the 1999 rate of tuberculosis is 6.4 cases per 100,000 population (CDC: Reported Tuberculosis in the United States, 1999). The 1999 rate of tuberculosis in RA patients in the US has been reported to be 6.2 cases per 100,000 regardless of the use of DMARDs or corticosteroids, which is similar to the rate of tuberculosis in the US population. In contrast, the rate of tuberculosis in RA patients who have received infliximab therapy has been reported to be 24.4 cases per 100,000, which is about 4-fold higher than in the US population (Keane J, et al. *N Engl J Med.* 2001;345:1098-1104). In Japan, it has been reported that the standardized incidence ratio for tuberculosis in RA patients is 3.98 based on comparison with the general population and moreover, the incidence rate of tuberculosis is higher in RA patients treated with anti-TNF therapy than in RA patients untreated with anti-TNF therapy (5.5-fold higher in RA patients treated with infliximab; 1.4-fold higher in RA patients treated with etanercept) (Tanaka Y, et al. *Kekkaku*. 2010;85:33-45).

Though the conditions for assessment are different from those in the above-mentioned studies, according to the pooled data from tofacitinib phase III studies, while tuberculosis was not reported in the tofacitinib 5 mg group or the adalimumab group, the incidence rate of tuberculosis was high in the tofacitinib 10 mg group. Given the above-mentioned mechanism of development of tuberculosis and the increased rate of tuberculosis among patients treated with anti-TNF agents, patients should be tested for tuberculosis infection prior to administration of tofacitinib, like anti-TNF agents, and the relevant statements will be included in the warnings and precautions sections (contraindications, careful administration, important precautions) of the package insert.

PMDA considers as follows:
It has been suggested that tofacitinib inhibits major cytokines involved in the defense against tuberculosis infection more extensively, compared with anti-TNF agents, which are known to be associated with an increased risk of tuberculosis, and actually, the incidence rate of tuberculosis tended to be higher in the tofacitinib 10 mg group than in the adalimumab group. Taking account of these findings, it is necessary to take strict precautions against the development of tuberculosis during treatment with tofacitinib. It is necessary to ensure that the medical practice understands that the risk of tuberculosis associated with tofacitinib is comparable to or greater than that with anti-TNF agents and then provide adequate cautions to ensure that the safety measures, like those for anti-TNF agents (screening test for tuberculosis prior to administration of tofacitinib, collaboration with physicians who have experience in the diagnosis and treatment of infections such as tuberculosis, etc.) are complied with.

4.(iii).B.(2).1).(b) Malignancy

The applicant explained the occurrence of malignancies (excluding non-melanoma skin cancer [NMSC]) as follows:

According to the pooled data from phase III studies and the pooled data from long-term extension studies, the exposure-adjusted incidence rates of malignancies were as shown in Table 62.

Table 62. Exposure-adjusted incidence rate of malignancies (excluding NMSC)
(Phase III studies[a)] [0-12 months], Long-term extension studies[b)])

	Phase III studies				Long-term extension studies	
	Tofacitinib 5 mg (n = 1216)	Tofacitinib 10 mg (n = 1214)	Placebo (n = 681)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1321)	Tofacitinib 10 mg (n = 1906)
n (%)	5 (0.4)	8 (0.7)	0	1 (0.5)	23 (1.7)	12 (0.6)
Incidence rate (/100 patient-years) [95% CI]	0.55 [0.23, 1.33]	0.88 [0.44, 1.76]	0	0.56 [0.08, 3.97]	1.03 [0.68, 1.55]	1.36 [0.77, 2.40]

a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041

Based on the pooled data from phase II, phase III, and long-term extension studies (4816 subjects who received at least one dose of tofacitinib), the duration of exposure to tofacitinib prior to the diagnosis of malignancy was examined for 50 tofacitinib-treated subjects with malignancies (excluding NMSC). As a result, as shown in Table 63, the incidence rate of malignancies tended to increase after 12 months of treatment. The most common types of malignancy were lung cancer (12 subjects) and breast cancer (9 subjects) and gastric cancer was reported in Japanese subjects only (3 subjects). Six deaths due to malignancies were reported, which included 2 deaths due to lung cancer, 1 death due to breast cancer, 1 death due to colon cancer, and 1 death due to ovarian cancer in the tofacitinib 5 mg group and 1 death due to malignant lung and hepatic neoplasms in the tofacitinib 10 mg group. Although the information on the disease stage at the time of diagnosis was obtained from a limited number of subjects and a definitive discussion is impossible, 2 subjects each had stage II, III, and IV disease and there were subjects who had advanced disease with metastases at the time of diagnosis.

Table 63. Incidence rates of malignancies (excluding NMSC) over time and disease stage at the time of diagnosis (Phase II, Phase III, and long-term extension studies[a])

Duration of exposure	Overall (n = 4789)	0-6 months (n = 4789)	6-12 months (n = 3817)	12-18 months (n = 2649)	18-24 months (n = 992)	>24 months (n = 709)	
% (n)	1.0% (50)	0.3% (16)	0.3% (12)	0.3% (8)	0.5% (5)	1.3% (9)	
Incidence rate (/100 patient-years) [95% CI]	0.89 [0.67, 1.17]	0.75 [0.46, 1.23]	0.73 [0.41, 1.28]	0.97 [0.48, 1.94]	1.28 [0.53, 3.08]	1.37 [0.71, 2.63]	
						>24 months	>30 months
		Metastatic lung adenocarcinoma 10 mg	Non-small cell lung cancer 5 mg+MTX	Lung adenocarcinoma 10 mg	Malignant lung neoplasm 5 mg	Endometrial cancer (Stage III C) 5 mg+MTX	Breast cancer 5 mg+MTX
		Non-small cell lung cancer 10 mg	Metastatic lung cancer 5 mg+MTX	Metastatic small cell lung cancer 10 mg+MTX	Malignant lung neoplasm and metastases to liver 5 mg	Central nervous system lymphoma 5 mg+MTX	Breast cancer (Stage II) 5 mg+MTX
		Breast cancer 10 mg+MTX	Malignant lung and hepatic neoplasms 10 mg+MTX	Breast cancer and metastases to lymph nodes 5 mg	Paget's disease of the breast 5 mg+MTX	Laryngeal cancer 5 mg+MTX	Ovarian cancer 5 mg+MTX
		Squamous cell carcinoma of the cervix 10 mg+MTX	Breast cancer 10 mg	Breast cancer 10 mg+MTX	Ovarian cancer (Stage IV) 5 mg+MTX	Thyroid cancer 5 mg	Vulval cancer 5 mg+MTX
		Cervix carcinoma 10 mg+MTX	Breast cancer 10 mg+MTX/Sulf	Renal neoplasm 5 mg+MTX	Liposarcoma 5 mg		Gallbladder cancer 5 mg
		Colon neoplasm 1 mg+MTX	Metastatic breast cancer 5 mg+MTX	Bronchial carcinoma (Stage IV) 5 mg+MTX			
		Gastric cancer and metastases to lymph nodes 5 mg+MTX	Choroid plexus papilloma 5 mg	Prostate cancer 10 mg+LEF			
		Metastatic neoplasm 10 mg+MTX	Colon cancer 5 mg	Malignant melanoma 10 mg+MTX			
		Renal cell carcinoma (Stage II) 10 mg	Gastric cancer 5 mg				
		Metastatic renal cell carcinoma 5 mg+MTX	Gastric cancer 5 mg				
		Prostate cancer 10 mg+MTX	Lymphoma (Stage IIIA) 10 mg+MTX				
		Metastatic prostate cancer and metastases to bone marrow 10 mg+MTX	Lymphoproliferative disorder 5 mg				
		Squamous cell carcinoma 10 mg	Bronchial carcinoma 10 mg+MTX				
		Metastatic squamous cell carcinoma 5 mg+MTX					
		Melanocytic naevus 5 mg+MTX					

Diagnosis (disease stage), Treatment group
a) A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044, A3921045, A3921046, A3921064, A3921109

The standardized incidence ratio (SIR) for malignancies (excluding NMSC) in the pooled phase II, phase III, and long-term extension studies was 1.11 (95%CI, 0.82-1.47) based on comparison with the SEER (Surveillance Epidemiology and End Result) database, which was not substantially higher than the SIR (0.9-

1.1) in the US RA patient population and the incidence rate was within the range of the incidence rates of malignancies (excluding NMSC) in RA patients treated with biologics (0.30-1.77/100 patient-years) or DMARDs (0.56-1.30/100 patient-years) based on published data.[43]

According to the pooled data from phase III studies and the pooled data from long-term extension studies, the exposure-adjusted incidence rates of lymphomas were as shown in Table 64.

Table 64. Exposure-adjusted incidence rate of lymphomas
(Phase III studies[a)] [0-12 months], Long-term extension studies[b)])

	Phase III studies				Long-term extension studies	
	Tofacitinib 5 mg (n = 1216)	Tofacitinib 10 mg (n = 1214)	Placebo (n = 681)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1321)	Tofacitinib 10 mg (n = 1906)
n (%)	0	1 (<0.1)	0	0	2 (0.2)	0
Incidence rate (/100 patient-years) [95% CI]	0	0.11 [0.02, 0.78]	0	0	0.09 [0.02, 0.36]	0

a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041

RA patients have been shown to be at higher risk of Hodgkin's lymphoma and non-Hodgkin's lymphoma etc. when compared to the general population (Khurana R, et al. *J Rheumatol*. 2008;35:1704-1708, Smitten AL, et al. *Arthritis Res Ther.* 2008;10:R45). Although lymphomas were observed in a monkey 39-week toxicity study of tofacitinib, lymphomas occurred in only 3 subjects (1 of 3030 subjects in the pooled phase III studies, 2 of 3227 subjects in the pooled long-term extension studies) in clinical studies.[44] The SIR for lymphomas in the pooled phase II, phase III, and long-term extension studies was 1.74 (95% CI, 0.36-5.10) based on comparison with the SEER database, which was not substantially higher than the SIR (1.1-9.7) in the US RA patient population and was not substantially different from the SIR in RA patients or RA patients treated with biologics based on published data.[45]

Since there is no sufficient evidence that tofacitinib at clinical doses reduces immune surveillance and tofacitinib was not mutagenic in genotoxicity studies etc., it is considered that the development of malignancies and lymphomas in patients treated with tofacitinib is not attributable to the mode of action of tofacitinib, but is caused by aging or RA itself. However, as the incidence rates of malignancies and lymphomas with tofacitinib are at present estimated to be comparable to those with biologics, relevant information will be included in the important precautions section of the package insert.

A considerable number of cases of malignancies reported in the tofacitinib group in Japanese and foreign clinical studies were diagnosed at an advanced stage. PMDA asked the applicant to explain the possibility that tofacitinib promotes the progression of malignancy and that clinical symptoms of malignancy are masked by tofacitinib therapy.

[43] Thomas E, et al. *Int J Cancer*. 2000;88:497-502, Wolfe F, et al. *Arthritis Rheum.* 2007;56:2886-2895, Beauparlant P. *Semin Arthritis Rheum.* 1999;29:148-158, Smitten AL, et al. *Arthritis Res Ther.* 2008;10:R45, Cibere J. *Arthritis Rheum.* 1997;40:1580-1586, Askling J, et al. *Arthritis Rheum.* 2005;52:1986-1992.
[44] Data cut-off date of March 29, 2011
[45] Gridley, et al. *J Natl Cancer Inst.* 1993;85:307-311, Ekstrom K, et al. *Arthritis Rheum.* 2003;48:963-970, Geborek, et al. *Ann Rheum Dis*. 2005;4:699-703, Franklin, et al. *Arthritis Rheum.* 2007;56:790-798, Wolfe F, et al. *Arthritis Rheum.* 2007;56: 2886-2895, Smitten AL, et al. *Arthritis Res Ther.* 2008;10:R45.

The applicant explained as follows:
It has been reported that cancer symptoms such as pain and malaise are related to IL-6 (Laird BJ, et al. *Pain*. 2011;152:460-463) and tofacitinib may mask various symptoms of malignancy by inhibiting IL-6 signaling mediated by JAK1/2. However, taking also into account that it has been reported that IL-6 plays an important role in increased rates of malignancy associated with an enhanced inflammatory response, tumor cell resistance to immune surveillance, and cancer cell stimulation through an autocrine feedback loop (Koh E, et al. *Int J Surg Pathol.* 2012;20:233-239, Johnson C, et al. *Transl Gastrointest Cancer.* 2012;1:58-70), JAK inhibition is not considered to contribute to tumor progression.

PMDA considers as follows:
Based on the currently available data, no conclusion can be drawn regarding the risk of malignancy associated with tofacitinib. However, as shown in Table 62, the exposure-adjusted incidence rate of malignancies was higher with tofacitinib than with placebo and there was a trend towards a dose- and exposure duration-dependent increase in the incidence rate of malignancies. Thus, the risk of malignancy associated with tofacitinib can not be ruled out. The exposure-adjusted incidence rate of malignancies tended to be higher in the tofacitinib 10 mg group also when compared to the adalimumab group and furthermore, concerning the reported cases of malignancies following treatment with tofacitinib, 28 of 50 subjects were diagnosed with malignancy at an early phase (within 1 year after the start of treatment) and 15 of 50 subjects were already at an advanced stage or had metastatic lesions at the time of diagnosis. Taking account of these findings, the possibility that tofacitinib promotes the development of malignancy or masks various symptoms of malignancy can not be ruled out. Therefore, special attention should be paid to the possible development of malignancy during treatment with tofacitinib and especially when administering 10 mg of tofacitinib, extreme caution is needed. The risk of lymphoma associated with tofacitinib is anticipated since over-immunosuppression is known to be associated with the development of lymphoma. Although a trend towards dose-dependency of the incidence rate of lymphomas was not observed in clinical studies, given that serious infections, which are also considered associated with immunosuppression, tended to occur dose-dependently, it is very likely that high-dose tofacitinib or tofacitinib in combination with immunosuppressive, anti-rheumatic drugs or corticosteroids, etc. will result in an increased risk of lymphoma. Based on the above, it is necessary to provide adequate caution about the possibility that tofacitinib is associated with the risk of malignancy and lymphoma and in addition to the safety measures proposed by the applicant, the development of malignancies should be described also in the warnings section of the package insert, like existing biologics. The occurrence of malignancies and lymphoma should be compared between tofacitinib and existing drugs via post-marketing long-term surveillance study etc.

The appropriateness of the clinical use of tofacitinib 10 mg needs to be determined carefully, also from the point of view of the risk of malignancy and lymphoma.

4.(iii).B.(2).1).(c) Gastrointestinal perforations
The applicant explained the occurrence of gastrointestinal perforations as follows:
According to the pooled data from phase III studies and the pooled data from long-term extension studies, the exposure-adjusted incidence rates of gastrointestinal perforations were as shown in Table 65.

According to the pooled data from phase II, phase III, and long-term extension studies (4816 subjects who received at least one dose of tofacitinib), among 10 subjects with gastrointestinal perforations, 1 subject each had prior or concurrent gastric ulcer, gastric perforation, and diverticulitis, which were considered associated with gastrointestinal perforation (a total of 3 subjects). Five of the ten cases were reported as diverticular perforation. Nine subjects were taking concomitant NSAIDs, 8 subjects were taking concomitant glucocorticoids, and 8 subjects were taking concomitant MTX. Given that the use of NSAIDs or glucocorticoids is an important risk factor for gastrointestinal perforations (Wolfe F, et al. *J Rheumatol.* 2000;27:1668-1673, Silverstein FE, et al. *JAMA.* 2000;284:1247-1255, Cannon CP, et al. *Lancet.* 2006;368:1771-1781, Laine L, et al. *Lancet.* 2007;369:465-473, Laine L, et al. *Gastroenterology.* 2008;135:1517-1525), the events of gastrointestinal perforations observed following treatment with tofacitinib may have been related to concomitant medications. Furthermore, the exposure-adjusted incidence rates of gastrointestinal perforations based on the pooled data from phase III studies and the pooled data from long-term extension studies were similar to the rates for biologics or DMARDs in RA patients (0.05-0.11/100 patient-years) based on published data and the rate for tocilizumab (anti-IL-6 receptor antibody), which is associated with higher risk of gastrointestinal perforation compared with other biologics, in RA patients (0.28/100 patient-years) (van Vollenhoven, et al. *Arthritis Rheum.* 2009;60 Suppl 10:1613). Thus, tofacitinib is unlikely to be associated with an increased incidence rate of gastrointestinal perforations.

Gastrointestinal perforations will be listed as clinically significant adverse reactions in the package insert to alert physicians.

Table 65. Exposure-adjusted incidence rate of gastrointestinal perforations
(Phase III studies[a] [0-12 months], Long-term extension studies[b])

	Phase III studies				Long-term extension studies	
	Tofacitinib 5 mg (n = 1216)	Tofacitinib 10 mg (n = 1214)	Placebo (n = 681)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1321)	Tofacitinib 10 mg (n = 1906)
n (%)	0	2 (0.2)	0	0	4 (0.3)	3 (0.2)
Incidence rate (/100 patient-years) [95% CI]	0	0.22 [0.06, 0.88]	0	0	0.18 [0.07, 0.48]	0.34 [0.11, 1.06]

a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041

PMDA considers as follows:

Although the events of gastrointestinal perforations observed following treatment with tofacitinib may have been related to NSAIDs or glucocorticoids, which are often concomitantly used in RA patients, given that tofacitinib inhibits IL-6 signaling, like tocilizumab, which is associated with higher risk of gastrointestinal perforation and that the incidence rate of gastrointestinal perforations with tofacitinib was comparable to that with tocilizumab, it is necessary to provide adequate caution about gastrointestinal perforations and in addition to listing gastrointestinal perforations as clinically significant adverse reactions in the package insert, careful administration of tofacitinib should be recommended in patients with intestinal diverticulum, which is considered a risk factor for gastrointestinal perforation, like tocilizumab. It is also necessary to collect information on the occurrence of gastrointestinal perforations and the demographics and characteristics of patients who have experienced gastrointestinal perforations etc. and further investigate its relationship to

tofacitinib via post-marketing surveillance.

4.(iii).B.(2).1).(d) Interstitial pneumonia

The applicant explained the occurrence of interstitial lung disease as follows:

According to the pooled data from phase III studies and the pooled data from long-term extension studies, the exposure-adjusted incidence rates of interstitial lung disease were as shown in Table 66.

According to the pooled data from phase II, phase III, and long-term extension studies (4816 subjects who received at least one dose of tofacitinib), 11 subjects were diagnosed with interstitial lung disease, including 8 female subjects. The number of subjects by race was as follows: 1 Japanese subject, 5 non-Japanese Asian subjects, and 5 non-Asian foreign subjects. One subject (Japanese) died and the cause of death was thrombotic thrombocytopenic purpura and a relationship between interstitial pneumonia and death could not be determined. All of the 11 subjects were taking other RA treatments that are known to be associated with interstitial lung disease (MTX, prednisone, prednisolone, salazosulfapyridine), of whom 1 subject had presented with slight fibrotic changes on chest X-ray at baseline.

Table 66. Exposure-adjusted incidence rate of interstitial lung disease
(Phase III studies[a)] [0-12 months], Long-term extension studies[b)])

	Phase III studies				Long-term extension studies[c)]	
	Tofacitinib 5 mg (n = 1216)	Tofacitinib 10 mg (n = 1214)	Placebo (n = 681)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1321)	Tofacitinib 10 mg (n = 1906)
n (%)	1 (<0.1)	1 (<0.1)	1 (0.2)	0	1 (<0.1)	4 (0.2)
Incidence rate (/100 patient-years) [95% CI]	0.11 [0.02, 0.79]	0.11 [0.02, 0.78]	0.49 [0.07, 3.51]	0	0.05 [0.01, 0.32]	0.45 [0.17, 1.21]

a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041
c) One subject with interstitial lung disease prior to the start of a long-term extension study (in a Phase II study) was not included in the analysis.

PMDA considers as follows:

Although treatment-emergent interstitial lung disease may have been related to other RA treatments, the possibility that tofacitinib in combination with other RA treatments is associated with even higher risk of interstitial lung disease can not be ruled out and the proportion of Asian subjects among all subjects with interstitial lung disease tended to be high. Thus, it should be stated in the package insert etc. that interstitial pneumonia may occur during treatment with tofacitinib. It is also necessary to continue to investigate a relationship between tofacitinib and interstitial pneumonia, including the association with risk factors such as concomitant medications, via post-marketing surveillance etc.

4.(iii).B.(2).1).(e) Cytopenia

Based on the pharmacological effect of tofacitinib (inhibition of hematopoietic growth factor signaling), it is anticipated that tofacitinib may induce cytopenia [see "3.(i) Summary of pharmacology studies"].

(1) Decreases in leukocyte counts (neutrophil and lymphocyte counts)

The applicant explained the occurrence of decreases in leukocyte counts (neutrophil and lymphocyte counts) including its association with the incidence of serious infections as follows:

Concerning changes in neutrophil counts over time in the pooled phase III studies, tofacitinib 5 mg, tofacitinib

10 mg, and adalimumab resulted in decreases in neutrophil counts from baseline over the first month of treatment without further declines at Month 3 and thereafter. The decrease was greater with tofacitinib 10 mg than with tofacitinib 5 mg (Figure 6).

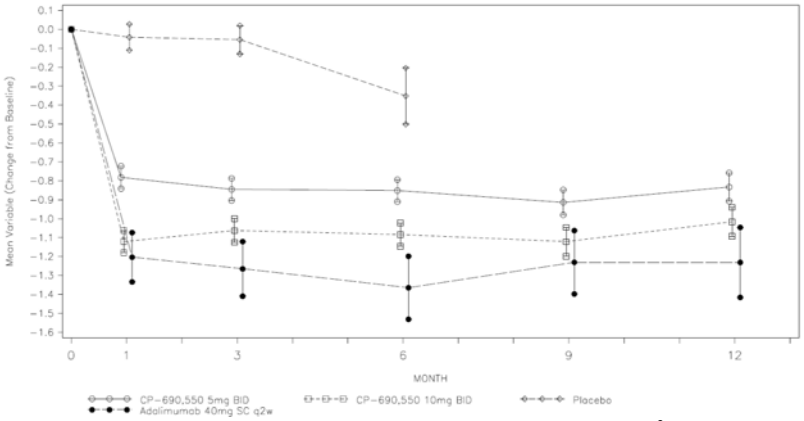


Figure 6. Changes from baseline in neutrophil counts (×1000/mm^3, Mean ± SE)
0-12 months in phase III studies (A3921032, A3921044, A3921045, A3921046, A3921064)
CP-690,550 refers to tofacitinib.

Concerning changes in lymphocyte counts over time in the pooled phase III studies, tofacitinib 5 mg, tofacitinib 10 mg, and adalimumab resulted in increases in lymphocyte counts from baseline for the first month. Lymphocytosis was sustained up to Month 12 in the adalimumab group. In contrast, lymphocytosis was transient and lymphocyte counts declined gradually at Month 3 and thereafter in the tofacitinib groups (Figure 7).

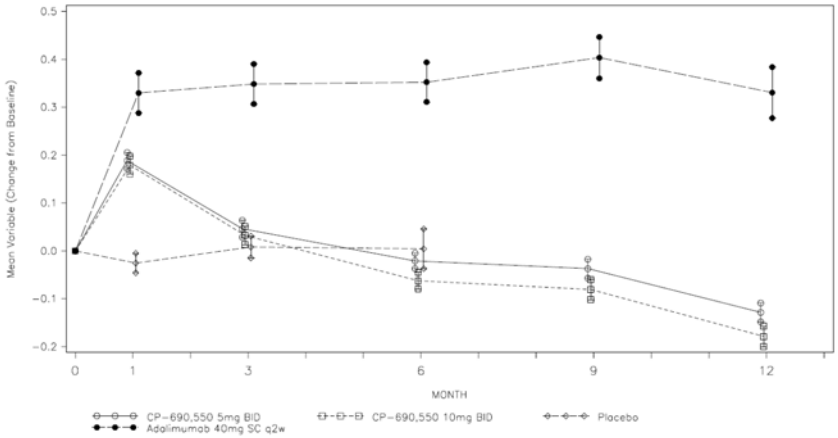


Figure 7. Changes from baseline in lymphocyte counts (×1000/mm^3, Mean ± SE)
0-12 months in phase III studies (A3921032, A3921044, A3921045, A3921046, A3921064)
CP-690, 550 refers to tofacitinib.

Based on the pooled data from long-term extension studies, the proportion of subjects who developed serious infections and the proportion of subjects treated for infections by severity of neutropenia or lymphopenia were examined. As shown in Table 67, there was no association between the severity of neutropenia and the proportion of subjects who developed serious infections or the proportion of subjects treated for infections, whereas the proportion of subjects who developed serious infections and the proportion of subjects treated for infections were both higher among subjects with lymphocyte counts <500/mm^3 compared with subjects without lymphopenia.

Table 67. Proportion of subjects who developed serious infections and proportion of subjects treated for infections by severity of neutropenia or lymphopenia (Long-term extension studies[a])

	Proportion of subjects who developed serious infections		Proportion of subjects treated for infections	
	Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 5 mg	Tofacitinib 10 mg
Neutrophil count				
Normal	3.9 (49/1251)	2.3 (42/1852)	27.5 (344/1251)	21.5 (398/1852)
Mild neutropenia (≥1500 and <2000/mm^3)	0 (0/60)	2.5 (1/40)	20.0 (12/60)	27.5 (11/40)
Moderate to severe neutropenia (≥500 and <1500/mm^3)	12.5 (1/8)	0 (0/8)	37.5 (3/8)	0 (0/8)
Life-threatening neutropenia (<500/mm^3)	0 (0/0)	0 (0/0)	0 (0/0)	0 (0/0)
Lymphocyte count				
Normal	3.8 (8/210)	2.3 (18/784)	22.9 (48/210)	20.8 (163/784)
Mild lymphopenia (≥1500 and <2000/mm^3)	3.0 (10/330)	1.9 (10/520)	23.0 (76/330)	21.2 (110/520)
Moderate to severe lymphopenia (≥500 and <1500/mm^3)	3.9 (30/773)	2.2 (13/592)	29.8 (230/773)	22.5 (133/592)
Life-threatening lymphopenia (<500/mm^3)	33.3 (2/6)	50.0 (2/4)	83.3 (5/6)	75.0 (3/4)

% (n)
a) A3921024, A3921041

Based on the above, the proportion of subjects who developed serious infections and the proportion of subjects treated for infections were both higher among subjects who developed life-threatening lymphopenia (lymphocyte counts <500/mm^3) compared with subjects without lymphopenia. Thus, physicians will be alerted about the association between lymphopenia and serious infections and advised to monitor lymphocyte counts periodically and tofacitinib will be contraindicated in patients with a lymphocyte count <500/mm^3. Periodic monitoring of neutrophil counts will also be advised and tofacitinib will be contraindicated in patients with a neutrophil count <500/mm^3.

PMDA considers as follows:
Although there was no association between neutropenia and infections, neutrophil counts <1500/mm^3 were observed in long-term extension studies and the incidence of infections across the studies was high. Taking account of these findings, it is necessary to provide adequate caution about neutropenia as well as lymphopenia.

(2) Hemoglobin decreases (including anaemia)

The applicant explained the occurrence of treatment-emergent hemoglobin decreases and anaemia and relevant safety measures as follows:
Concerning the events of hemoglobin decreases in the pooled phase III studies and the pooled long-term extension studies, the proportion of subjects by degree of hemoglobin decrease was as shown in Table 68. The incidence of any degree of hemoglobin decreases was higher in the tofacitinib 5 mg group than in the tofacitinib 10 mg group, which is considered attributable to longer duration of total exposure in the 5 mg group than in the 10 mg group.

Table 68. Proportion of subjects by degree of hemoglobin decrease
(Phase III studies[a)] [0-3 months], Long-term extension studies[b)])

	Phase III studies					Long-term extension studies		
	Tofacitinib 5 mg (n = 1220)	Tofacitinib 10 mg (n = 1217)	Tofacitinib All doses (n = 2437)	Placebo (n = 681)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1319)	Tofacitinib 10 mg (n = 1900)	Tofacitinib All doses (n = 3219)
Mild to Moderate[c)]	35 (2.9)	58 (4.8)	93 (3.8)	29 (4.3)	2 (<1.0)	169 (12.8)	158 (8.3)	327 (10.2)
Severe[d)]	3 (<1.0)	6 (<1.0)	9 (<1.0)	1 (<1.0)	0	37 (2.8)	22 (1.2)	59 (1.8)
Life-threatening[e)]	0	1 (<1.0)	1 (<1.0)	1 (<1.0)	0	17 (1.3)	6 (<1.0)	23 (<1.0)

n (%)
a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041
c) Hemoglobin decrease from baseline ≥1 to ≤2 g/dL
d) Hemoglobin decrease from baseline >2 to <3 g/dL or absolute value >7 and <8 g/dL
e) Hemoglobin decrease from baseline ≥3 g/dL or absolute value ≤7 g/dL

Concerning the events of anaemia in the pooled phase III studies (0-3 months), the incidences of adverse events of anaemia were 1.2% (15 of 1216 subjects) in the tofacitinib 5 mg group, 1.1% (13 of 1214 subjects) in the tofacitinib 10 mg group, and 1.2% (8 of 681 subjects) in the placebo group and the exposure-adjusted incidence rates were 5.22/100 patient-years in the tofacitinib 5 mg group, 4.50/100 patient-years in the tofacitinib 10 mg group, and 5.07/100 patient-years in the placebo group. Most of the adverse events were mild in severity and severe anaemia was reported by only 1 subject in the tofacitinib 10 mg group in 3 to 6 months. According to the pooled data from long-term extension studies, anaemia occurred in 2.7% of the tofacitinib 5 mg group (36 of 1321 subjects) and 1.1% of the tofacitinib 10 mg group (21 of 1906 subjects) and the exposure-adjusted incidence rates were 1.62/100 patient-years in the tofacitinib 5 mg group and 2.41/100 patient-years in the tofacitinib 10 mg group. Based on the above, there were no major differences in the incidence rate of anaemia between tofacitinib and placebo and no clear dose-relatedness was observed.

Concerning safety measures against hemoglobin decreases and anaemia, although there was no association between the occurrence of these events and prior or concurrent anaemia and related events in clinical studies, taking account of the pharmacological effect of tofacitinib and the occurrence of hemoglobin decreases in clinical studies, tofacitinib will be contraindicated in patients who have hemoglobin levels <8 g/dL and periodic monitoring of anaemia-related parameters, such as hemoglobin, will be advised in the package insert.

PMDA considers as follows:
Although clinical studies suggested no association between prior or concurrent anaemia and the occurrence of treatment-emergent adverse events of hemoglobin decreases and anaemia, since these events are as expected from the pharmacological effect of tofacitinib (inhibition of hematopoietic growth factor signaling) and the prevalence of anaemia in RA patients is high, as the applicant proposed, patients should be tested for anaemia and signs of anaemia, etc. prior to starting tofacitinib and close attention should be paid to changes in hemoglobin levels, etc. and the possible development/exacerbation of anaemia, etc. also during treatment with tofacitinib. It is also necessary to further investigate the occurrence of hemoglobin decreases and anaemia, including risk factors, via post-marketing surveillance.

(3) Thrombocytopenia and pancytopenia

The applicant explained changes in platelet counts during treatment with tofacitinib as follows:

According to the pooled data from phase III studies, changes from baseline in platelet counts were as shown in Figure 8 and tofacitinib 5 mg, tofacitinib 10 mg, and adalimumab led to decreases from baseline in platelet counts at Month 1 without further declines at Month 3 and thereafter. Long-term extension studies also showed a similar trend. However, as platelet counts declined, but remained within the normal range, there is no need to advise monitoring of platelet counts, etc. in the package insert etc.

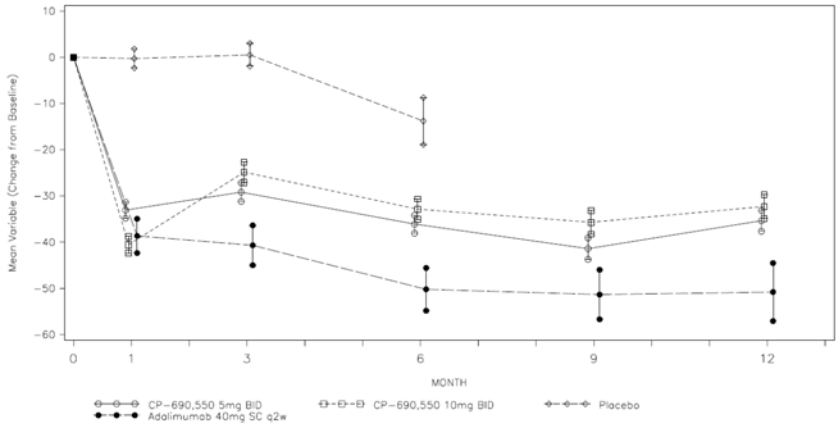


Figure 8. Changes from baseline in platelet counts (×1000/mm^3, Mean ± SE)
0-12 months in phase III studies (A3921032, A3921044, A3921045, A3921046, A3921064)
CP-690,550 refers to tofacitinib.

PMDA considers as follows:

According to the pooled data from phase III studies, decreases in platelet counts from baseline of 30,000 to 40,000/mm^3 were observed in the tofacitinib groups and 4 subjects each had thrombocytopenia leading to discontinuation and a serious adverse event of thrombocytopenia. One subject in the tofacitinib 10 mg group had pancytopenia leading to discontinuation in a global phase III study (A3921044) and 1 subject in the tofacitinib 5 mg group had a serious adverse event of pancytopenia in long-term extension studies (A3921024/A3921041). Although the relationship of these events to tofacitinib is not clear, as the possibility that tofacitinib, e.g. when combined with DMARDs, which are also associated with the risk of cytopenia, mutually increases the risk of thrombocytopenia can not be ruled out, it is necessary to carefully watch the trend of occurrence of thrombocytopenia and pancytopenia as well as decreases in hemoglobin and leukocyte counts via post-marketing surveillance and continue to examine the need for alerting.

4.(iii).B.(2).1).(f) Lipid abnormalities

The applicant explained the occurrence of lipid abnormalities as follows:

According to the pooled data from phase III studies, significant dose-dependent increases from baseline in LDL cholesterol occurred at Month 1 (Figure 9) and remained stable up to Month 12 in the tofacitinib 5 mg and 10 mg groups. Also in the pooled long-term extension studies, similar increases in LDL cholesterol occurred in the tofacitinib 5 mg and 10 mg groups. Other lipid parameters (apolipoprotein B-100, HDL cholesterol, ApoA I) also tended to increase. The percent change from baseline in LDL cholesterol at Month 3 was 4.33%, 14.01%, and 18.72% in the placebo, tofacitinib 5 mg, and tofacitinib 10 mg groups, respectively, in a tofacitinib monotherapy study (A3921045) and −0.54%, 13.75%, and 17.56% in the placebo, tofacitinib

5 mg, and tofacitinib 10 mg groups, respectively, in background DMARD studies (A3921032, A3921044, A3921046, A3921064). In clinical studies of tocilizumab (monotherapy), which is known to be associated with lipid abnormalities, in RA patients, the percent change from baseline in LDL cholesterol at Month 3 has been reported to be 20.6% (published data in the registration application for tocilizumab) and LDL cholesterol levels increased to a lesser extent with tofacitinib compared with tocilizumab.

According to the pooled data from phase III studies (0-3 months), the incidences of adverse events of lipid abnormalities were 3.1% (76 of 2430 subjects) in the overall tofacitinib group and 1.2% (8 of 681 subjects) in the placebo group and the incidence tended to be higher with tofacitinib, but all of the adverse events were mild or moderate in severity and no serious adverse events were reported. According to the pooled data from long-term extension studies, the exposure-adjusted incidence rates of events of lipid abnormalities classified under the system organ class, "Investigations" were 1.6/100 patient-years in the tofacitinib 5 mg group and 1.8/100 patient-years in the tofacitinib 10 mg group and the exposure-adjusted incidence rates of those classified under the system organ class, "Metabolism and nutrition disorders" were 4.2/100 patient-years in the tofacitinib 5 mg group and 6.1/100 patient-years in the tofacitinib 10 mg group. These adverse events were all mild or moderate in severity and no serious adverse events were reported. One subject in the tofacitinib 5 mg group was discontinued from treatment due to an adverse event of a lipid abnormality.

Based on the changes in lipid parameters and the occurrence of lipid abnormalities in the pooled phase III studies and the pooled long-term extension studies as described above, periodic monitoring of total cholesterol, LDL cholesterol, and HDL cholesterol will be advised in the package insert.

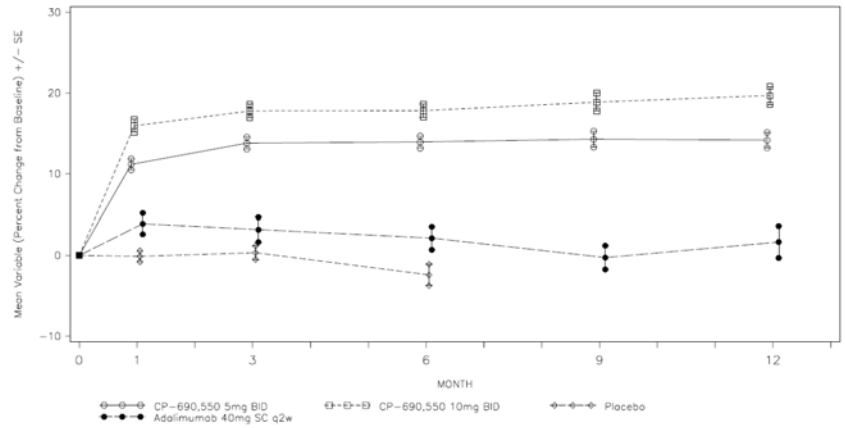


Figure 9. Percent change from baseline in LDL cholesterol (%, Mean ± SE)
0-12 months in phase III studies (A3921032, A3921044, A3921045, A3921046, A3921064)
CP-690,550 refers to tofacitinib.

PMDA asked the applicant to explain whether clinical studies suggested a relationship between elevations of LDL cholesterol and cardiovascular adverse events.

The applicant explained as follows:
According to the pooled data from phase III studies and the pooled data from long-term extension studies, LDL cholesterol levels over time in subjects with cardiovascular events or congestive cardiac failure were largely similar to those in the overall population and the occurrence of cardiovascular adverse events was as shown in Table 69. As LDL cholesterol levels were within the normal range or below the lower limit of the

normal range in all subjects, elevations of LDL cholesterol are unlikely to be related to the occurrence of cardiovascular events. Based on published data, the incidence rates of serious cardiovascular adverse events with tocilizumab have been reported to be 0.36/100 patient-years for myocardial infarction and 0.22/100 patient-years for cerebral infarction (published data in the registration application for tocilizumab), which are not substantially different from those with tofacitinib.

Table 69. Exposure-adjusted incidence rate of cardiovascular adverse events
(Phase III studies[a)] [0-12 months], Long-term extension studies[b)])

		Phase III studies				Long-term extension studies	
		Placebo (n = 681)	Tofacitinib 5 mg (n = 1216)	Tofacitinib 10 mg (n = 1214)	Adalimumab (n = 204)	Tofacitinib 5 mg (n = 1321)	Tofacitinib 10 mg (n = 1906)
Cardiovascular death	n	0	0	2	1	1	0
	Incidence rate (/100 patient-years) [95% CI]	0	0	0.22 [0.06, 0.88]	0.56 [0.08, 3.97]	0.06 [0.01, 0.41]	0
Non-fatal myocardial infarction	n	0	2	2	2	1	0
	Incidence rate (/100 patient-years) [95% CI]	0	0.22 [0.06, 0.89]	0.22 [0.06, 0.88]	1.12 [0.28, 4.47]	0.06 [0.01, 0.41]	0
Non-fatal cerebrovascular accidents	n	2	3	2	0	1	2
	Incidence rate (/100 patient-years) [95% CI]	0.99 [0.25, 3.95]	0.33 [0.11, 1.03]	0.22 [0.06, 0.88]	0	0.06 [0.01, 0.41]	0.23 [0.06, 0.91]
Congestive cardiac failure	n	0	0	5	0	2	0
	Incidence rate (/100 patient-years) [95% CI]	0	0	0.55 [0.23, 1.32]	0	0.12 [0.03, 0.46]	0

a) A3921032, A3921044, A3921045, A3921046, A3921064
b) A3921024, A3921041

PMDA largely accepts the applicant's explanation. Meanwhile, given that RA patients often use corticosteroids, which cause hyperlipidaemia as an adverse effect and that it has also been suggested that RA itself may be a risk factor for arteriosclerosis, the possibility that abnormal lipid parameters associated with tofacitinib increases the risk of cardiovascular events can not be ruled out. Thus, it is necessary to collect long-term information and investigate the relationship between abnormal lipid parameters and cardiovascular adverse events via post-marketing surveillance etc.

4.(iii).B.(2).1).(g) Hepatic function abnormalities

The applicant explained the occurrence of transaminase elevations and hepatic adverse events as follows:
According to the pooled data from phase III studies and the pooled data from long-term extension studies, increases in ALT of >3 times the upper limit of normal after the start of treatment were uncommon. The incidences of increases in ALT of >3 times the upper limit of normal were 0.6% (6 of 1090 subjects) in the tofacitinib 5 mg group and 0.5% (6 of 1101 subjects) in the tofacitinib 10 mg group in the pooled phase III studies and 0.5% (6 of 1205 subjects) in the tofacitinib 5 mg group and 0.5% (9 of 1692 subjects) in the tofacitinib 10 mg group in the pooled long-term extension studies.[46]

Based on the pooled data from phase III studies, the incidences and severities of adverse events in the SMQ (Standardized MedDRA Query) of hepatobiliary disorders (hepatic cyst, hepatic function abnormal, hepatitis, enlarged liver, etc.) and liver test abnormalities were examined according to the patient characteristics. When

[46] Data from subjects with normal baseline.

examined according to the dose of MTX, the incidences of hepatobiliary disorders among tofacitinib-treated subjects were 1.0% (4 of 407 subjects), 0% (0 of 686 subjects), and 0.6% (3 of 506 subjects) in the subgroups of MTX dose at baseline ≤10 mg/week, >10 and ≤15 mg/week, and >15 mg/week, respectively, and the incidences of liver test abnormalities were 2.2% (9 of 407 subjects), 1.7% (12 of 686 subjects), and 2.2% (11 of 506 subjects), respectively, and there were no differences according to MTX dose and most of these events were mild or moderate in severity in all subgroups. In the subgroups on tofacitinib monotherapy, background MTX therapy, and background DMARD therapy, the incidences of hepatobiliary disorders among tofacitinib-treated subjects were 0.4% (2 of 488 subjects), 0.4% (7 of 1621 subjects), and 0.6% (11 of 1942 subjects), respectively, and there were no differences in the incidence or severity among these subgroups. Meanwhile, the incidences of liver test abnormalities among tofacitinib-treated subjects were 0.6% (3 of 488 subjects), 2.0% (32 of 1621 subjects), and 2.4% (47 of 1942 subjects), respectively, and the incidences of severe liver test abnormalities were 0% (0 of 488 subjects), 0.12% (2 of 1621 subjects), and 0.15% (3 of 1942 subjects), respectively, and a trend towards increased incidence and severity of liver test abnormalities in the subgroup on background MTX therapy or background DMARD therapy was observed. In the subgroups with and without prior treatment with biologics, the incidences of hepatobiliary disorders among tofacitinib-treated subjects were 0.4% (1 of 239 subjects) and 0.5% (12 of 2191 subjects), respectively and the incidences of liver test abnormalities were 2.5% (6 of 239 subjects) and 2.0% (44 of 2191 subjects), respectively, and there were no differences according to prior treatment with biologics and most of these events were mild or moderate in severity in both subgroups.

The proportion of Japanese RA patients with increases in AST or ALT of >3 times the upper limit of normal after the start of treatment and the major patient characteristics in 3 Japanese studies (A3921039, A3921040, A3921041) and a global phase III study (A3921044) were as shown in Table 70. In Japanese RA patients, high baseline AST or ALT, concomitant use of multiple anti-RA drugs including MTX, and concomitant NSAID or isoniazid may have been associated with transaminase elevations.

Table 70. Proportion of Japanese RA patients with increases in AST or ALT of >3 times the upper limit of normal and major patient characteristics

	Tofacitinib 1 mg	Tofacitinib 3 mg	Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 15 mg	Placebo
No. of subjects with increases in AST or ALT of >3 times the upper limit of normal						
n (%)	1/81 (1.2)	1/80 (1.3)	13/464 (2.8)	8/192 (4.2)	1/54 (1.9)	2/104 (1.9)
Major patient characteristics						
Baseline AST or ALT >40 U/L	0/1	1/1	6/13	4/8	1/1	1/2
Concomitant NSAID	1/1	1/1	13/13	8/8	1/1	2/2
Concomitant corticosteroids	1/1	1/1	10/13	7/8	1/1	1/2
Concomitant MTX	0/1	0/1	12/13	8/8	0/1	0/2
Concomitant isoniazid	0/1	0/1	5/13	3/8	1/1	2/2

a) Japanese subjects in A3921039, A3921040, A3921041, and A3921044

Based on the above, since the incidence and severity of liver test abnormalities tended to increase with background DMARD or MTX therapy compared with tofacitinib monotherapy and concomitant use of multiple anti-RA drugs including MTX and concomitant NSAID or isoniazid may have been associated with transaminase elevations in Japanese subjects, monitoring of transaminase levels when tofacitinib is used concomitantly with drugs potentially causing hepatic function disorders, etc., will be advised in the package insert.

PMDA considers as follows:

Since the information on tofacitinib in combination with various DMARDs in clinical studies and the information on tofacitinib in combination with high-dose MTX in Japanese RA patients are limited, it is necessary to continue to investigate the occurrence of hepatic function disorders, including the association with risk factors such as concomitant medications, via post-marketing surveillance.

4.(iii).B.(2).1).(h) Increases in blood creatine kinase levels

The applicant explained the occurrence of increases in blood creatine kinase (CK) levels and rhabdomyolysis/myopathy as follows:

According to the pooled data from phase III studies, there was a trend towards dose-dependent increases in blood CK levels in subjects treated with tofacitinib and the mean blood CK levels at Month 12 were 129 IU/L in the overall tofacitinib group and 85 IU/L in the adalimumab group.

According to the pooled data from phase III studies (0-3 months), the incidences of adverse events of increased blood CK levels were 0.7% (9 of 1216 subjects) in the tofacitinib 5 mg group and 2.1% (26 of 1214 subjects) in the tofacitinib 10 mg group, which tended to be higher than 0.4% (3 of 681 subjects) in the placebo group and 0.5% (1 of 204 subjects) in the adalimumab group. The exposure-adjusted incidence rates were 3.13/100 patient-years in the tofacitinib 5 mg group and 9.01/100 patient-years in the tofacitinib 10 mg group and a trend towards dose-dependent increases was observed. According to the pooled data from long-term extension studies, the incidences of adverse events of increased blood CK levels were 2.0% (27 of 1321 subjects) in the tofacitinib 5 mg group and 1.0% (19 of 1906 subjects) in the tofacitinib 10 mg group and the exposure-adjusted incidence rates were 1.21/100 patient-years in the tofacitinib 5 mg group and 2.18/100 patient-years in the tofacitinib 10 mg group.

The temporal association between elevated levels of CK and the onset of rhabdomyolysis/myopathy was examined. As a result, according to the pooled data from phase III studies and the pooled data from long-term extension studies, an adverse event suggestive of myopathy or rhabdomyolysis occurred within ±7 days of elevation of CK ≥5 times the upper limit of normal in 1 of 1906 subjects in the tofacitinib 10 mg group in the pooled long-term extension studies. Rhabdomyolysis occurred in 1 of 1906 subjects in the tofacitinib 10 mg group in the pooled phase III studies. This subject had rhabdomyolysis, renal failure, congestive cardiac failure, and pulmonary hypertension on Day 357 with elevation of CK on Days 363 to 370 and the elevated levels of CK were considered associated with poor perfusion of the kidney and muscles/intestine due to severe pulmonary hypertension and decreased cardiac output. The subject died due to respiratory failure on Day 374 and a causal relationship of rhabdomyolysis to tofacitinib could not be denied. Myopathy occurred in 2 of 3227 subjects treated with tofacitinib in the pooled long-term extension studies. One of them had asymptomatic myopathy and CK levels returned to normal after tofacitinib dose reduction from 10 mg to 5 mg and did not increase following the resumption of treatment with tofacitinib 10 mg. The other subject had elevation of CK (385 U/L) on Day 562 before the onset of myopathy (Day 743), but CK levels at the onset of myopathy were within the normal range. A causal relationship of myopathy to tofacitinib could not be denied for both cases. The above results suggested no association between elevated levels of CK and the occurrence of rhabdomyolysis/myopathy and the package insert will contain the information on elevations of CK only and there is no need to specifically caution about rhabdomyolysis/myopathy.

As the association between elevations of blood CK levels related to treatment with tofacitinib and rhabdomyolysis/myopathy is not clear at present, PMDA accepts the applicant's explanation that a specific caution about rhabdomyolysis/myopathy will not be included in the package insert. However, as there was a trend towards dose-dependent increases in blood CK levels in subjects treated with tofacitinib and rhabdomyolysis and myopathy for which a causal relationship to tofacitinib could not be denied were also reported, PMDA considers that it is necessary to further investigate the possibility that elevations of blood CK levels induce clinically significant changes such as rhabdomyolysis and myopathy via post-marketing surveillance and provide the obtained information to clinical practice as appropriate.

4.(iii).B.(2).1).(i) Increases in serum creatinine levels and renal dysfunction etc.

The applicant explained the occurrence of increases in serum creatinine (Cr) levels and renal dysfunction etc. as follows:

According to the pooled data from phase III studies, serum Cr levels increased from baseline by Month 3 in subjects treated with tofacitinib (Figure 10). Serum Cr levels increased slowly also after Month 3 and plateaued gradually and the increases from baseline at Month 12 were approximately 0.06 mg/dL in the tofacitinib 5 mg group and approximately 0.08 mg/dL in the tofacitinib 10 mg group.

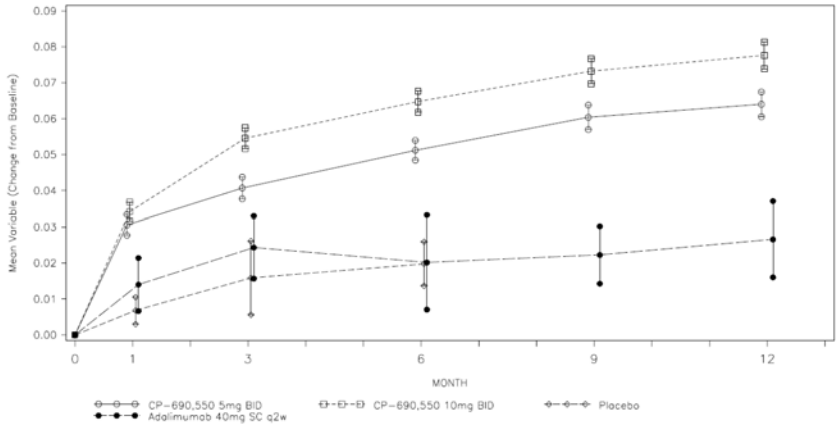


Figure 10. Changes from baseline in serum Cr levels (mg/dL, Mean ± SE)
0-12 months in phase III studies (A3921032, A3921044, A3921045, A3921046, A3921064)
CP-690,550 refers to tofacitinib.

In a tofacitinib monotherapy study (A3921045), the changes from baseline in serum Cr at Month 6 were 0.06 mg/dL in the tofacitinib 5 mg group and 0.08 mg/dL in the tofacitinib 10 mg group. On the other hand, in a global phase III study (A3921044) and foreign phase III studies (A3921032, A3921046, A3921064) of tofacitinib in combination with DMARDs including MTX, the changes from baseline in serum Cr at Month 6 were 0.05 mg/dL in the tofacitinib 5 mg group and 0.06 mg/dL in the tofacitinib 10 mg group. Serum Cr levels increased with either tofacitinib monotherapy or combination therapy.

Concerning the events of renal dysfunction in the pooled phase III studies (0-3 months), the incidences of adverse events identified by the SMQ of acute renal failure (renal failure, acute renal failure, renal impairment, proteinuria, blood Cr abnormal or increased, blood urea increased, protein urine present, etc.) were 0.3% (4 of 1216 subjects) in the tofacitinib 5 mg group, 0.6% (7 of 1214 subjects) in the tofacitinib 10 mg group, 0.1% (1 of 681 subjects) in the placebo group, and 1.0% (2 of 204 subjects) in the adalimumab group. Although the

incidence was slightly higher with tofacitinib compared with placebo, most of the events were blood Cr increased, and renal failure or acute renal failure was not reported. The exposure-adjusted incidence rates were 1.39/100 patient-years in the tofacitinib 5 mg group and 2.43/100 patient-years in the tofacitinib 10 mg group.

According to the pooled data from long-term extension studies, the incidences of adverse events identified by the SMQ of acute renal failure were 2.9% (38 of 1321 subjects) in the tofacitinib 5 mg group and 1.0% (20 of 1906 subjects) in the tofacitinib 10 mg group and most of the events were blood Cr increased. The exposure-adjusted incidence rates were 1.72/100 patient-years in the tofacitinib 5 mg group and 2.30/100 patient-years in the tofacitinib 10 mg group.

Based on the above, the package insert will contain the information on serum Cr increases only and there is no need to specifically caution about acute renal failure.

As there was no association between Cr increases and clinically significant renal dysfunction such as acute renal failure in clinical studies, PMDA accepts the applicant's explanation that a specific caution about acute renal failure will not be included in the package insert. However, tofacitinib administration resulted in dose-dependent increases in Cr levels, and drugs associated with the risk of renal dysfunction such as MTX and NSAIDs are often used concomitantly in RA patients and the possibility that tofacitinib and concomitant medications mutually increase the risk of renal dysfunction can not be ruled out. Thus, it is necessary to continue to investigate the occurrence of renal dysfunction associated with tofacitinib, including the association with risk factors such as concomitant medications, via post-marketing surveillance and provide the obtained information to clinical practice as appropriate.

4.(iii).B.(3) Dosage and administration

4.(iii).B.(3).1) Justification for increasing the dose of tofacitinib to 10 mg

Concerning the proposed dosage and administration for tofacitinib, the applicant explained the basis for considering that the usual dose is 5 mg and the dose can be increased to 10 mg according to the patient's condition, as follows:

The results from 5 Japanese and foreign phase III studies of tofacitinib in RA patients (A3921032, A3921044, A3921046, A3921064, A3921045) demonstrated the efficacy of tofacitinib at doses of 5 and 10 mg in improving signs and symptoms of RA such as joint pain and furthermore, ACR70 response rate and the rate of DAS28 <2.6 were higher with tofacitinib 10 mg than with tofacitinib 5 mg.

On the other hand, regarding the safety of tofacitinib, based on the results of non-clinical and clinical studies, as adverse events to be noted, serious infections such as herpes zoster and tuberculosis, malignancies including lymphomas, gastrointestinal perforations, cardiovascular events, interstitial lung disease, and laboratory abnormalities (decreases in neutrophil count, lymphocyte count, and hemoglobin etc., increases in lipid parameters such as LDL cholesterol, increases in transaminases, serum creatinine, and creatine kinase) were reported. Meanwhile, the safety profiles of tofacitinib 5 or 10 mg as a monotherapy or in combination with DMARDs were largely similar to those of existing biologics or DMARDs in RA patients and these adverse events can be adequately managed by appropriate patient selection and screening, periodic monitoring, and

medical management as appropriate. However, given that the incidence of adverse events tended to be higher with tofacitinib 10 mg than with tofacitinib 5 mg, it is recommended that tofacitinib should be initiated at 5 mg and continued for a certain period of time and then, the dose should be increased to 10 mg after considering the risks and benefits for each patient. Thus, the appropriate dosage and administration statement is as follows: "The usual dosage is 5 mg of tofacitinib given orally twice daily. The dose can be increased to 10 mg twice daily according to the patient's condition."

PMDA considers as follows:
From an efficacy point of view, ACR70 response rate and the rate of DAS28 <2.6 etc. tended to be higher with tofacitinib 10 mg than with tofacitinib 5 mg and it is understood that the 10 mg dose may be more useful for some patients. However, dose-dependent increases in adverse events were observed in subjects treated with tofacitinib and especially, the incidence rates of life-threatening adverse events, i.e. serious infections and malignancies, tended to be higher in the tofacitinib 10 mg group than in the tofacitinib 5 mg group (Table 56 and Table 62), the incidence rates of tuberculosis and malignancies tended to be higher in the tofacitinib 10 mg group than in the adalimumab group (Table 61 and Table 62), the incidence rate of serious infections associated with tofacitinib tended to be higher in the Asian population including Japanese subjects compared with other racial groups (Table 58), and furthermore, tofacitinib 10 mg tended to be less well tolerated by Japanese RA patients compared with foreign RA patients in terms of the incidence of adverse events and the incidence of adverse events leading to discontinuation etc. (Table 55). Taking account of these findings, it is hard to conclude from the currently available clinical study data that the benefits of increasing the dose of tofacitinib from 5 mg to 10 mg, i.e. improvement in signs and symptoms of RA such as joint pain, outweigh the potential risks and it is difficult to approve a proposed dose of 10 mg BID for Japanese RA patients.

Tofacitinib 5 mg BID for Japanese RA patients is acceptable. However, it has been suggested that even tofacitinib 5 mg BID is associated with a higher incidence rate of serious infections as compared with adalimumab, a similar incidence rate of malignancies to adalimumab, and a similar trend of occurrence of gastrointestinal perforations, cardiovascular events, and laboratory abnormalities etc. as compared with existing biologics. Therefore, safety measures equivalent to those for existing biologics (warnings of serious infections and malignancies, restrictions on prescribing physicians and medical institutions, etc.) should be required also for clinical use of tofacitinib 5 mg BID.

4.(iii).B.(3).2) Dosage and administration in special populations
As described above, PMDA considers that a proposed dose of 10 mg BID is not approvable. The applicant recommended that tofacitinib dose should not exceed 5 mg BID in patients with severe renal impairment, patients with moderate hepatic impairment, and in cases of coadministration with strong CYP3A4 inhibitors such as ketoconazole or moderate CYP3A4 and strong CYP2C19 inhibitors such as fluconazole, etc., due to the potential for high systemic exposures [see "4.(ii) Summary of clinical pharmacology studies"]. Thus, PMDA asked the applicant to reconsider dose recommendations for tofacitinib in these patient populations.

The applicant explained as follows:
The $AUC_{0-\infty}$ values in subjects with severe renal impairment and subjects with moderate hepatic impairment

were 2.23-fold and 1.65-fold higher, respectively, than those in subjects with normal renal or hepatic function [see "4.(ii) Summary of clinical pharmacology studies"] and the $AUC_{0-\infty}$ values following administration of tofacitinib 5 mg in these subjects were estimated to be almost comparable to those following administration of tofacitinib 10 mg in subjects with normal renal or hepatic function. Thus, it was recommended that tofacitinib dose should not exceed 5 mg BID in patients with the potential for high systemic exposures, including patients with severe renal impairment or moderate hepatic impairment. However, taking account of PMDA's opinion on the approvability of the proposed doses of tofacitinib, the dose should be reduced to 5 mg QD (equivalent to half the daily AUC at 5 mg BID) in patients with moderate or severe renal impairment, patients with moderate hepatic impairment, and in cases of coadministration with strong CYP3A4 inhibitors or CYP2C19 inhibitors, or CYP3A4 and CYP2C19 inhibitors.

PMDA considers as follows:
Although the applicant's response regarding dose recommendations for tofacitinib in the above special populations is acceptable, a final conclusion will be made, taking account of comments from the Expert Discussion on the appropriateness of approving a proposed dose of 5 mg BID only.

4.(iii).B.(4) Clinical positioning of tofacitinib

4.(iii).B.(4).1) Clinical positioning of tofacitinib relative to existing drugs

PMDA asked the applicant to explain the clinical positioning of tofacitinib relative to existing drugs.

The applicant explained as follows:
As all of phase II (A3921025, A3921039) and phase III (A3921044, A3921064) studies in patients who had a previous inadequate response to MTX, phase II (A3921035, A3921040) and phase III (A3921045, A3921046) studies in patients who had a previous inadequate response to DMARDs, and a phase III study in patients who had a previous inadequate response to anti-TNF agents (A3921032) demonstrated the efficacy of tofacitinib, it is considered that robust efficacy of tofacitinib in RA patients who have had an inadequate response to existing therapies has been demonstrated. Furthermore, in a foreign phase III study using adalimumab, one of existing anti-TNF agents, as an active comparator (A3921064), tofacitinib showed similar efficacy and safety profile as adalimumab, and tofacitinib is an oral agent and more convenient. Therefore, tofacitinib will become a useful therapeutic option for RA patients who have had an inadequate response to existing therapies.

PMDA considers as follows:
Based on the patient populations included in clinical studies and these clinical study data to date, positioning tofacitinib as a drug to be used in RA patients who have had an inadequate response to existing DMARDs including MTX, like the positioning of existing biologics, is appropriate. However, given that tofacitinib is considered associated with similar risks as biologics (e.g. the risk of serious infections etc. and a concern about inducing malignancies), the medical practice should be adequately advised to carefully determine whether to use tofacitinib, according to the patient's condition etc., after both the physician and patient fully take account of the balance of risks and benefits of tofacitinib vs. existing therapies, so that tofacitinib will not be used casually, just because it is an oral agent.

4.(iii).B.(4).2) Choice between using tofacitinib as a monotherapy or in combination with MTX etc.

PMDA asked the applicant to explain their view on the choice between using tofacitinib as a monotherapy or in combination with DMARDs including MTX and the order of priority.

The applicant explained as follows:

The results from a series of phase III studies including 1 monotherapy study (A3921045), 3 background MTX studies (A3921032, A3921044, A3921064), and 1 background DMARD study[47] (A3921046) demonstrated the efficacy of tofacitinib either as a monotherapy or in combination with DMARDs including MTX in RA patients who had a previous inadequate response to existing DMARDs [see "4.(iii).A *Summary of the submitted data*"]. Also in Japanese RA patients, the results from Japanese phase II studies (A3921039, A3921040) and a global phase III study (A3921044) were as shown in Table 71, which demonstrated the efficacy of tofacitinib either as a monotherapy or in combination with MTX. Regarding safety, although the incidences of herpes zoster and transaminase elevations tended to be higher with tofacitinib in combination with DMARDs including MTX than with tofacitinib monotherapy [see "4.(iii).B.(2) Safety"], other safety profiles were similar between monotherapy and combination therapy.

Table 71. Comparison of the effects of tofacitinib 5 mg and 10 mg in reducing signs and symptoms of RA such as joint pain at Month 3 (FAS, Japanese population)

Endpoint	Treatment group	A3921039[a)]	A3921040[a)]	A3921044[b)]
		Tofacitinib + MTX	Tofacitinib monotherapy	Tofacitinib + MTX
ACR20 response rate[c)]	Placebo	14.29 (4/28)	15.38 (8/52)	20.83 (5/24)
	Tofacitinib 5 mg	96.30 (26/27)	73.08 (38/52)	59.57 (28/47)
	Tofacitinib 10 mg	80.77 (21/26)	84.91 (45/53)	65.96 (31/47)
ACR50 response rate[c)]	Placebo	14.29 (4/28)	7.69 (4/52)	8.33 (2/24)
	Tofacitinib 5 mg	81.48 (22/27)	46.15 (24/52)	46.81 (22/47)
	Tofacitinib 10 mg	57.69 (15/26)	69.81 (37/53)	55.32 (26/47)
ACR70 response rate[c)]	Placebo	3.57 (1/28)	1.92 (1/52)	0.00 (0/24)
	Tofacitinib 5 mg	33.33 (9/27)	26.92 (14/52)	23.40 (11/47)
	Tofacitinib 10 mg	34.62 (9/26)	49.06 (26/53)	36.17 (17/47)
DAS28-4(ESR) <2.6[d)]	Placebo	8.33 (2/24)	0.00 (0/48)	6.25 (1/16)
	Tofacitinib 5 mg	33.33 (8/24)	16.00 (8/50)	14.71 (5/34)
	Tofacitinib 10 mg	42.86 (9/21)	42.86 (21/49)	31.25 (10/32)

% (n)
a) At Month 3
b) At Month 6, Results from the Japanese subpopulation
c) The LOCF imputation method was used in Study A3921039 and Study A3921040 and the NRI method was used in Study A3921044.
d) No imputation was applied to missing data in Study A3921039 and Study A3921040 and the NRI method was used in Study A3921044.

Concerning the choice between using tofacitinib as a monotherapy or in combination with DMARDs including MTX and the order of priority, no clinical studies have directly compared tofacitinib monotherapy with combination therapy and rigorous evaluation is difficult. However, given that MTX is positioned as a standard treatment in the current treatment paradigms for RA, tofacitinib, like biologics, will be used primarily in patients who have had an inadequate response to MTX and according to the patient's condition, tofacitinib in combination with DMARDs (primarily MTX) or as a monotherapy will be chosen.

[47] Tofacitinib was given in combination with DMARDs (mostly MTX).

PMDA considers as follows:
Although no clinical studies have directly compared tofacitinib monotherapy with tofacitinib in combination with DMARDs including MTX, no major differences in efficacy between tofacitinib as a monotherapy and in combination with MTX etc. have been suggested (Table 47 and Table 71), and regarding safety, tofacitinib is considered associated with similar risks as biologics and furthermore, tofacitinib has safety concerns common to DMARDs, such as the risk of infections, cytopenia, liver function test abnormalities, and renal function test abnormalities, and the possibility that tofacitinib in combination with DMARDs increases the risk of these events can not be ruled out. Thus, tofacitinib in combination with DMARDs should not be used casually and the medical practice should be adequately advised to ensure adequate monitoring if tofacitinib has to be used in combination with DMARDs.

4.(iii).B.(5) Indications
PMDA considers as follows:
With respect to the proposed indications of "rheumatoid arthritis in patients who have not adequately responded to conventional treatments (including prevention of structural damage to joints and improvement in physical function)," a claim of "rheumatoid arthritis in patients who have not adequately responded to conventional treatments" is approvable because the efficacy of tofacitinib in reducing signs and symptoms of RA such as joint pain, a major clinical symptom, has been demonstrated. However, as for a claim of prevention of structural damage to joints, as discussed in "4.(iii).B.(1) Efficacy," based on the data from a global phase III study (A3921044), the primary analysis of change from baseline in mTSS did not confirm the superiority of tofacitinib 5 mg over placebo and pairwise comparison showed a statistically significant difference between tofacitinib 10 mg and placebo, which was considered to be driven by subjects with clinically unlikely degrees of change. Based on these results etc., it is difficult to conclude that the efficacy of tofacitinib in preventing joint structural damage was demonstrated. Therefore, it is difficult to approve a claim of prevention of structural damage to joints in the application. Since improvement in physical function is considered incidental to reduction in joint symptoms, etc., it is unnecessary to specially mention it as a distinct claim.

In conclusion, based on the statement in the package insert for biologics, it should be stated in the precautions of indications section of the package insert for tofacitinib that tofacitinib may be used in patients in whom clinical symptoms due to the disease remain even after appropriate treatment with at least one other disease-modifying antirheumatic drug (DMARD) etc. and then the indication statement for tofacitinib in Japan should be modified as shown below. A final conclusion will be made, taking account of comments from the Expert Discussion.

[Indication]
Rheumatoid arthritis in patients who have not adequately responded to conventional treatments

4.(iii).B.(6) Post-marketing safety measures
PMDA considers as follows:

Since the occurrence of adverse events of serious infections (herpes zoster, tuberculosis, etc.), malignancies, gastrointestinal perforations, cytopenia, and lipid abnormalities, etc. is similar between tofacitinib and existing biologics, safety measures equivalent to those for existing biologics (the use of tofacitinib should be limited to physicians with adequate knowledge about tofacitinib and experience in treatment of rheumatoid arthritis; warnings of serious infections and malignancies; screening for tuberculosis prior to starting tofacitinib should be advised, etc.) should be taken. In addition, as tofacitinib has been shown to be teratogenic in toxicity studies [see "3.(iii) Summary of toxicology studies"], tofacitinib should be contraindicated in pregnant women or in women who may possibly be pregnant and if tofacitinib is used in women of childbearing potential, contraception must be ensured during treatment and for a certain period of time after treatment. Furthermore, given that JAK1/3 is widely distributed in the body and involved in the signaling of a variety of cytokines, the possibility that when tofacitinib is used to treat a larger number of patients, adverse events that were not captured in clinical studies occur, can not be ruled out. Thus, a drug use-results survey with physicians and all patients registered should be conducted in order to establish the safety profile of tofacitinib (including the detection of unknown adverse events) as soon as possible and a long-term surveillance study including a comparator group to follow patients during long-term treatment for the occurrence of serious infections, malignancies, and cardiovascular events associated with lipid abnormalities, etc. should also be conducted. Given that tofacitinib is an oral agent, it is important that patients themselves fully understand the risks of tofacitinib and the need for periodic tests and comply with the proper use of tofacitinib and regular visits. Therefore, it is also necessary to develop a patient's guide etc. describing the risks and benefits of tofacitinib in an appropriate and easy-to-understand manner. Moreover, information should be provided appropriately and promptly to healthcare providers and patients by sequentially disclosing post-marketing information via the internet etc.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application dossier.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1.2, 5.3.5.1.7, 5.3.5.1.8, 5.3.5.1.9, 5.3.5.2.1). As a result, protocol deviations (non-compliance with the prohibited concomitant medication restrictions and the requirement for prior therapy, failure to perform some of the tests, etc.) and inconsistencies between the source document and the CRF (clerical errors in entering assessment scores) were found at some trial sites.

The sponsor was found to have failed to appropriately detect some of the above-mentioned protocol deviations and inconsistencies between the source document and the CRF during monitoring visits.

Although the above findings requiring improvement were noted, PMDA concluded that the clinical studies as a whole were performed in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

With respect to the proposed indications of "rheumatoid arthritis in patients who have not adequately responded to conventional treatments (including prevention of structural damage to joints and improvement in physical function)," a claim of "rheumatoid arthritis in patients who have not adequately responded to conventional treatments" is approvable because the submitted data have demonstrated the efficacy of tofacitinib in reducing signs and symptoms of RA such as joint pain, it is difficult to approve a claim of prevention of structural damage to joints as it can not be concluded from the submitted study data that the efficacy of tofacitinib in preventing joint structural damage was demonstrated, and since improvement in physical function is considered incidental to reduction in joint symptoms, etc., it is unnecessary to specially mention it as a distinct claim. Concerning the proposed dosage and administration, tofacitinib 5 mg BID is considered to have clinical significance as a new therapeutic option for rheumatoid arthritis because its benefits have been shown to outweigh its potential risks, whereas it is difficult to conclude from the submitted data that the benefits of tofacitinib 10 mg BID have been shown to outweigh its potential risks. Regarding safety, as serious adverse drug reactions such as infections and malignancies may occur, rigorous safety measures, like those for biologics, should be taken. After the market launch, a drug use-results survey with physicians and all patients registered should be conducted in order to establish the safety profile of tofacitinib as soon as possible and a long-term surveillance study including a comparator group to follow patients during long-term treatment for the occurrence of serious infections, malignancies, and cardiovascular events associated with lipid abnormalities, etc. should also be conducted and the obtained information etc. should be provided sequentially to physicians and patients etc.

Provided that compliance with the above safety measures will be ensured, tofacitinib may be approved if, taking account of comments from the Expert Discussion, it can be concluded that there are no particular problems.

Review Report (2)

February 28, 2013

I. Product Submitted for Registration

[Brand name] Xeljanz Tablets 5 mg
[Non-proprietary name] Tofacitinib Citrate
[Name of applicant] Pfizer Japan Inc.
[Date of application] December 1, 2011

II. Content of the Review

The Expert Discussion and subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Dosage and administration

The proposed dosage and administration statement was "The usual dosage is 5 mg of tofacitinib given orally twice daily. The dose can be increased to 10 mg twice daily according to the patient's condition." However, as tofacitinib 10 mg BID has been suggested to be potentially associated with an increased risk of malignancy and serious infections etc. and its benefits have not been shown to outweigh its potential risks, PMDA concluded that a proposed dose of 5 mg BID only is approvable for Japanese RA patients. This conclusion by PMDA and the need for a post-marketing investigation of 10 mg BID and a lower dose of 3 mg BID etc. were discussed at the Expert Discussion.

The following comments were made by the expert advisors:

Although a clinically significant further effect of an increased dose of 10 mg BID may be expected, there are serious safety concerns about the 10 mg dose based on the currently available clinical study data and there is little necessity of taking the risk and choosing the 10 mg BID regimen. On the other hand, the safety of tofacitinib 5 mg BID also suggests that it is not well tolerated, but its risk can be managed as long as rheumatologists adequately experienced in the use of biologics use tofacitinib, and the use of tofacitinib 5 mg BID in Japanese RA patients is acceptable. However, given that after the market launch, tofacitinib is expected to be used also in RA patients with concomitant or previous illnesses etc., it is important to carefully assess the safety of tofacitinib 5 mg BID via post-marketing surveillance (e.g. determine if a greater risk than observed in clinical studies or a serious new risk arises). The need for tofacitinib 10 mg BID should be determined after the safety of tofacitinib 5 mg BID has been well established via post-marketing surveillance. Regarding the need for lower doses such as 3 mg BID, based on the data from phase II studies, adequate clinical efficacy may not be expected and an investigation of lower doses is not essential at present. However, the development of

lower doses should be considered for patients who have had intolerance to tofacitinib 5 mg BID or if post-marketing surveillance raises safety concerns about tofacitinib 5 mg BID.

Given that the incidence rate of serious infections associated with tofacitinib tended to be higher in the Asian population including Japanese subjects [see Review Report (1) "4.(iii).B.(2).1).(a).(1) Serious infections"], and that furthermore, low-body-weight, elderly patients with RA are common in Japan, the need for a lower dose than 5 mg BID, especially for low-body-weight patients, should be determined. PMDA asked the applicant to explain the effect of body weight on the pharmacokinetics and safety of tofacitinib.

The applicant explained as follows:
Concerning the effect of body weight on the pharmacokinetics of tofacitinib, based on the population pharmacokinetic model, AUC and C_{max} for a 40 kg patient were estimated to be 0.99-fold [0.73, 1.30] and 1.46-fold [1.36, 1.57], respectively, those of a 70 kg patient. Low-body-weight patients were estimated to have no major difference in AUC and an increase in C_{max}. Meanwhile, a logistic regression analysis of 4 Japanese and foreign phase II studies (A3921025, A3921035, A3921039, A3921040) was performed to examine the relationship between C_{max} and the incidence of adverse events, and as a result, the slope of the regression curve at around the geometric mean $C_{max,ss}$ of tofacitinib (5 mg BID) (58.6 ng/mL) is gentle and it is considered that an about 50% difference in the C_{max} does not significantly affect the incidence of adverse events. According to the pooled data from phase III studies, the incidence of adverse events by body weight was 50.9% (59 of 116 subjects) for <50 kg, 49.6% (263 of 530 subjects) for ≥50 kg and <70 kg, 54.0% (211 of 391 subjects) for ≥70 kg and <90 kg, and 50.8% (91 of 179 subjects) for ≥90 kg in the tofacitinib 5 mg group and 55.6% (69 of 124 subjects), 52.5% (271 of 516 subjects), 51.8% (197 of 380 subjects), and 59.8% (116 of 194 subjects), respectively, in the tofacitinib 10 mg group. There was no trend towards an increased incidence of adverse events, serious adverse events, or adverse events leading to discontinuation, etc. in low-body-weight patients. Based on the above, no dose adjustment for body weight is required.

Based on the above discussions and additional analysis for dose recommendation in low-body-weight patients, PMDA concluded as follows:
Provided that in addition to the safety measures as described in the Review Report (1), safety measures based on the results of a survey of all treated patients (described later) etc. are ensured [see "(3) Post-marketing safety measures"], the benefits of tofacitinib 5 mg BID outweigh its potential risks. The proposed dosage and administration statement should be changed as shown below.

Consequently, the applicant withdrew the 10 mg tablet from the application.

Although no dose adjustment is required in low-body-weight patients, since the incidence rate of serious infections was higher in the elderly [see Review Report (1) "4.(iii).B.(2).1).(a).(1) Serious infections"], tofacitinib exposure was increased in subjects with impaired hepatic or renal function [see Review Report (1) "4.(ii).A.(3) Intrinsic factor pharmacokinetic studies"], and the elderly often has reduced physiological function, it should be advised in the package insert that for elderly patients, a dose reduction should also be considered according to the patient's condition.

[Dosage and administration]
The usual dosage is 5 mg of tofacitinib given orally twice daily.

(2) Efficacy and indications
The following conclusion by PMDA was supported by the expert advisors:
Clinical study data have demonstrated the efficacy of tofacitinib in reducing signs and symptoms of RA such as joint pain. On the other hand, the currently available clinical study data have suggested the effectiveness of tofacitinib in preventing joint structural damage, but it is difficult to conclude that the efficacy of tofacitinib in preventing joint structural damage was confirmed.

Tofacitinib clinical studies were conducted in patients who had a previous inadequate response to MTX or DMARDs, which showed no major differences in safety profile between the two patient populations, and the efficacy and safety profile of tofacitinib 5 mg BID based on clinical study data are not considered substantially different from those of existing biologics. Therefore, PMDA concluded that like existing biologics, tofacitinib should be indicated for the "rheumatoid arthritis in patients who have not adequately responded to conventional treatments." Expert advisors' comments on this conclusion were sought, taking also into account that in the US, tofacitinib is indicated for the "treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to MTX."

The expert advisors commented that based on the patient populations included in clinical studies presented, the indication for tofacitinib should not be uniformly limited to patients who have had an inadequate response to MTX, and that tofacitinib should be indicated for the rheumatoid arthritis in patients who have not adequately responded to conventional treatments" and supported the conclusion by PMDA.

Based on the comments from the Expert Discussion, PMDA concluded as follows:
Tofacitinib should be indicated for the "rheumatoid arthritis in patients who have not adequately responded to conventional treatments." In the treatment of RA, there is a consensus that MTX is a standard treatment based on ample data on its efficacy and safety. Under the same indication, existing biologics have actually been used in patients who have had an inadequate response to MTX as a rule, excluding patients who have had intolerance to MTX. Thus, it should be stated in the precautions of indications section of the package insert that "tofacitinib may be used in patients in whom clinical symptoms due to the disease remain even after appropriate treatment with MTX or at least one other disease-modifying antirheumatic drug (DMARD)" so that the use of a standard treatment, MTX, will be fully considered before starting tofacitinib.

(3) Post-marketing safety measures

The following conclusions by PMDA were supported by the expert advisors:

Since the safety profile of tofacitinib is considered similar to those of existing biologics, safety measures equivalent to those for biologics (warnings of serious infections and malignancies, restrictions on prescribing physicians and medical institutions, etc.) should be taken. Furthermore, a drug use-results survey with physicians and all patients registered should be conducted in order to establish the safety profile of tofacitinib (including the detection of unknown adverse events) as soon as possible and a long-term surveillance study to follow patients during long-term treatment for the occurrence of serious infections, malignancies, and cardiovascular events associated with lipid abnormalities, etc. should also be conducted.

The expert advisors commented that registration for the survey should be limited to rheumatologists experienced in the use of biologics.

The following conclusion by PMDA was supported by the expert advisors:

The incidence rate of malignancies tended to be higher with tofacitinib compared with placebo or adalimumab. In addition, most cases of malignancies reported in the tofacitinib group were diagnosed early (within 1 year after the start of treatment) and a considerable number of cases of malignancies were already at an advanced stage or had metastatic lesions at the time of diagnosis. Taking account of these findings etc., special attention should be paid to the risk of malignancy and a post-marketing long-term surveillance study etc. that allows comparison of the occurrence of malignancies between tofacitinib and existing drugs should be conducted.

Furthermore, the following comment was made by the expert advisors:

The risk of malignancy associated with tofacitinib should be described more clearly (e.g. lymphoma and solid malignancies have been reported; and there was a trend towards a dose- and exposure duration-dependent increase in the incidence rate of malignancies) in the package insert and the materials for patients and for medical institutions, etc.

Based on the comment from the Expert Discussion, PMDA instructed the applicant to improve the statement in the package insert etc. cautioning about the risk of malignancy.

The applicant explained as follows:

The risk of malignancy will be described in the warnings and important precautions sections of the package insert and based on the latest information on the occurrence of malignancies (data cut-off date of September 29, 2011) as shown below, more specific information (there was a trend towards a dose-dependent increase in the incidence rate of malignancies associated with tofacitinib; the exposure-adjusted incidence rates [/100 patient-years] [95% CI] were 0.55 [0.23-1.33] in the tofacitinib 5 mg group and 0.88 [0.44-1.76] in the tofacitinib 10 mg group) will be included in the clinical studies section as well. Also in the materials for patients and for medical institutions, etc., the risk of malignancy will be described and other safety information will also be provided in an easy-to-understand manner.

Table 72. Incidence rates of malignancies (excluding NMSC) over time in clinical studies

(Phase II, Phase III, and long-term extension studies[a])

Duration of exposure	Overall (n = 4791)	0-6 months (n = 4791)	6-12 months (n = 4012)	12-18 months (n = 3126)	18-24 months (n = 2054)	24-30 months (n = 941)	30-36 months (n = 672)	>36 months (n = 567)
% (n)	1.4 (65)	0.4 (17)	0.3 (13)	0.4 (13)	0.4 (8)	0.7 (7)	0.7 (5)	0.4 (2)
Incidence rate (/100 patient-years) [95% CI]	0.94 [0.74, 1.20]	0.79 [0.49, 1.26]	0.72 [0.42, 1.24]	1.06 [0.61, 1.82]	1.09 [0.54, 2.17]	1.93 [0.92, 4.05]	1.60 [0.67, 3.84]	0.67 [0.17, 2.67]

a) A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044, A3921045, A3921046, A3921064, A3921109

In addition, PMDA instructed the applicant to plan a long-term surveillance study to follow patients during long-term treatment for the occurrence of serious infections, malignancies, and cardiovascular events associated with lipid abnormalities, etc., as well as a drug use-results survey with physicians and all patients registered and design the long-term surveillance study so that especially, the occurrence of malignancies can be compared between tofacitinib and existing biologics.

The applicant explained as follows:
A drug-use results survey with a 6-month observation period, covering all patients treated with tofacitinib, will be conducted until data from a certain number of cases (Target number of cases of 4000) will be collected. Also after the completion of the all-case surveillance, all patients surveyed will be observed for a total of 3 years. Anti-TNF agents will be used as a comparator (Target number of cases of 2000) for the surveillance study so that the risk of malignancy and serious infections during long-term treatment can be compared. Registration for the survey will be limited to rheumatologists experienced in the use of biologics. In patients treated with tofacitinib, the occurrence of serious infections (including herpes zoster and tuberculosis), malignancies (including lymphoma), gastrointestinal perforations, anaemia, interstitial pneumonia, cardiovascular adverse events, and hepatic dysfunction etc. will be investigated as priority items.

PMDA considers that the survey should be conducted as soon as possible and information should be provided appropriately and promptly to healthcare providers and patients by sequentially disclosing the latest information on the occurrence of malignancies and serious infections and other safety information etc. via the materials and the company's website, etc.

III. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the indication and the dosage and administration as shown below, with the following conditions. The re-examination period is 8 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication]
Rheumatoid arthritis in patients who have not adequately responed to conventional treatments

[Dosage and administration]
The usual dosage is 5 mg of tofacitinib given orally twice daily.

[Conditions for approval]
The applicant is required to:
1. Conduct a drug use-results survey after the market launch, covering all patients treated with the drug, until data from a certain number of cases will be collected, in order to collect data on the safety and efficacy of the drug as soon as possible and to take necessary measures to ensure proper use of the drug.
2. Conduct an appropriate post-marketing surveillance study to fully assess the safety of the drug and to evaluate the safety and efficacy of long-term use of the drug, including the occurrence of infections etc.