NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Tofacitinib Devatis 5 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 8.08 mg of tofacitinib citrate equivalent to 5 mg of tofacitinib free base active pharmaceutical ingredient.

Excipients with known effect
Contains sugars (lactose monohydrate).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Film coated tablet.
White, biconvex, round (8.0 mm diameter) film coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tofacitinib Devatis is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. Tofacitinib Devatis can be used alone or in combination with nonbiological disease-modifying antirheumatic drugs, including methotrexate.

Therapy with Tofacitinib Devatis should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.

4.2 Dose and Method of Administration

Tofacitinib Devatis may be used as monotherapy or in combination with methotrexate (MTX) or other nonbiological disease-modifying antirheumatic drugs (DMARDs). The recommended dosage is 5 mg administered twice daily.

Tofacitinib Devatis treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

Tofacitinib Devatis is given orally with or without food.

Dose Adjustments Due to Laboratory Abnormalities (see Section 4.4)

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia and anaemia as described in Table 1, Table 2 and Table 3 below. It is recommended that Tofacitinib Devatis not be initiated in patients with a lymphocyte count less than 0.5 x 10^9 cells/L.

Table 1: Dose Adjustments for Lymphopenia

Low Lymphocyte Count (see Section 4.4)	
Lab Value (x 10^9 cells/L)	**Recommendation**
Lymphocyte count ≥0.5	Maintain dose.
Lymphocyte count <0.5 (Confirmed by repeat testing)	Discontinue Tofacitinib Devatis

It is recommended that Tofacitinib Devatis not be initiated in patients with an absolute neutrophil count (ANC) <1.0 x 109 cells/L.

Table 2: Dose Adjustments for Neutropenia

Low Absolute Neutrophil Count (ANC) (see Section 4.4)	
Lab Value (x 10^9 cells/L)	**Recommendation**
ANC >1.0	Maintain dose.
ANC 0.5-1.0	For persistent decreases in this range, interrupt Tofacitinib Devatis dosing until ANC is >1.0. When ANC is >1.0, resume Tofacitinib Devatis 5 mg twice daily.
ANC <0.5 (Confirmed by repeat testing)	Discontinue Tofacitinib Devatis.

It is recommended that Tofacitinib Devatis not be initiated in patients with haemoglobin <90 g/L.

Table 3: Dose Adjustments for Anaemia

Low Haemoglobin Value (see Section 4.4)	
Lab Value (g/L)	**Recommendation**
≤20 g/L decrease and ≥90 g/L	Maintain dose.
>20 g/L decrease or <80 g/L (Confirmed by repeat testing)	Interrupt the administration of Tofacitinib Devatis until haemoglobin values have normalised.

Special Populations

Dosage Adjustment in Renal Impairment

No dose adjustment is required in patients with mild (creatinine clearance 51-80 mL/min) renal impairment. Tofacitinib Devatis dosage should be reduced to 5 mg once daily in patients with moderate (creatinine clearance 30-50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment (including but not limited to those with severe renal impairment who are undergoing haemodialysis) (see Section 4.4 and Section 5.2).

Dosage Adjustment in Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment. Tofacitinib Devatis dosage should be reduced to 5 mg once daily in patients with moderate hepatic impairment (see Section 4.4 and Section 5.2). Tofacitinib Devatis should not be used in patients with severe hepatic impairment (see Section 4.3 and Section 5.2).

Dose Adjustment due to Interactions with Other Medicines

Tofacitinib Devatis dosage should be reduced to 5 mg once daily in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole). Tofacitinib Devatis dosage should be reduced to 5 mg once daily in patients receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole). Co-administration of Tofacitinib Devatis with potent CYP inducers (e.g., rifampicin) may result in loss of or reduced clinical response (see Section 4.5). Co-administration of potent inducers of CYP3A4 with Tofacitinib Devatis is not recommended.

Dosage Adjustment in the Elderly

No dosage adjustment is required in patients aged 65 years and older.

Children and Adolescents

The safety and efficacy of tofacitinib in children aged from neonates to <18 years of age has not yet been established.

4.3 Contraindications

Hypersensitivity to tofacitinib citrate or to any of the excipients.

Tofacitinib Devatis must not be used in combination with biological DMARDs or other potent immunosuppressive agents such as azathioprine and ciclosporin.

Tofacitinib Devatis should not be used in patients with severe hepatic impairment.

4.4 Special Warnings and Precautions for Use

Therapy with Tofacitinib Devatis should be initiated and monitored by a rheumatologist or a specialist physician with expertise in the management of rheumatoid arthritis (RA).

Serious Infections

Patients treated with Tofacitinib Devatis are at increased risk for developing serious infections that may lead to hospitalisation or death, especially in those taking concomitant immunosuppressants.

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral or other opportunistic pathogens have been reported in RA patients receiving immunomodulatory agents (these include biological DMARDs as well as tofacitinib). The most common serious infections reported with tofacitinib included pneumonia, urinary tract infection, cellulitis, herpes zoster, bronchitis, septic shock, diverticulitis, gastroenteritis, appendicitis, and sepsis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infection, BK virus infections and listeriosis were reported with tofacitinib. Some patients have presented with disseminated rather than localised disease, and were often taking concomitant immunomodulating agents such as MTX or corticosteroids which, in addition to RA may predispose them to infections. Other serious infections, that were not reported in clinical studies, may also occur (e.g., coccidioidomycosis).

In one large randomised post-authorisation safety study (PASS) in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, a dose-dependent increase in serious infections was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1). Some of these serious infections resulted in death. Opportunistic infections were also reported in the study.

Tofacitinib Devatis should not be administered in patients with an active infection, including localised infections. The risks and benefits of treatment should be considered prior to initiating Tofacitinib Devatis in patients with chronic or recurrent infections, or those who have been exposed to tuberculosis, or with a history of a serious or an opportunistic infection, or have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or have underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Tofacitinib Devatis. Tofacitinib Devatis should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis (see Section 4.2). A patient who develops a new infection during treatment with Tofacitinib Devatis should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes (see Section 4.8).

Caution is also recommended in patients with a history of chronic lung disease as they may be more prone to infections (see Section 4.4, Interstitial Lung Disease).

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Discontinuation and monitoring criteria for lymphopenia are discussed in Section 4.2.

Tuberculosis

Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of Tofacitinib Devatis.

Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering Tofacitinib Devatis.

Antituberculosis therapy should be considered prior to administration of Tofacitinib Devatis in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a health care professional with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating antituberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Viral Reactivation

Viral reactivation has been reported with DMARD treatment and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with tofacitinib. In one large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, an increase in herpes zoster events was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1). Post-marketing cases of hepatitis B reactivation have been reported in patients treated with tofacitinib. The risk of herpes zoster is increased in patients treated with tofacitinib and appears to be higher in Japanese and Korean patients treated with tofacitinib.

The impact of tofacitinib on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with Tofacitinib Devatis.

Venous Thromboembolism

Venous thromboembolism (VTE) has been observed in patients taking tofacitinib in clinical trials and post-marketing reporting. In one large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, patients were treated with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily or a TNF inhibitor. A dose-dependent increase in pulmonary embolism (PE) events was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1). Many of these PE events were serious and some resulted in death. PE events were reported more frequently in this study in patients taking tofacitinib relative to other studies across the tofacitinib program (see Section 4.8 and Section 5.1).

Deep vein thrombosis (DVT) events were observed in all three treatment groups in this study (see Section 5.1).

Assess patients for VTE risk factors before starting treatment and periodically during treatment. Use Tofacitinib Devatis with caution in elderly patients and in patients in whom other risk factors are identified (see Section 4.2). Urgently evaluate patients with signs and symptoms of VTE. Discontinue tofacitinib while evaluating suspected VTE, regardless of dose or indication.

Major Adverse Cardiovascular Events (including Myocardial Infarction)

In one large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, patients were treated with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily or a TNF inhibitor. Major adverse cardiovascular events (MACE), including events of myocardial infarction, were observed in all three treatment groups in this study. An increase in non-fatal myocardial infarctions was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1). MACE, including events of myocardial infarction, were more common in older patients and in patients who were current or past smokers. Caution should be used in treating elderly patients, patients who are current or past smokers, and patients with other cardiovascular risk factors.

Malignancy and Lymphoproliferative Disorder (excluding Nonmelanoma Skin Cancer [NMSC])

Consider the risks and benefits of Tofacitinib Devatis treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated NMSC or when considering continuing Tofacitinib Devatis in patients who develop a malignancy. The possibility exists for tofacitinib to affect host defenses against malignancies. The impact of treatment with tofacitinib on the development and course of malignancies is not known, but malignancies were observed in clinical studies with tofacitinib.

Lymphomas have been observed in patients treated with tofacitinib and in patients treated with tofacitinib in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 5.1). Patients with RA, particularly those with highly active disease, are at a higher risk (up to several-fold) than the general population for the development of lymphoma, the role of tofacitinib, a Janus kinase (JAK) inhibitor, in the development of lymphoma is uncertain.

Lung cancers have been observed in patients treated with tofacitinib. Lung cancers were also observed in patients treated with tofacitinib in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor; an increase was observed in patients treated with tofacitinib 10 mg twice daily compared with TNF inhibitor (see Section 5.1). Of the 30 lung cancers reported in the study in patients taking tofacitinib, all but 2 were in patients who were current or past smokers. Patients with rheumatoid arthritis may be at higher risk than the general population for the development of lung cancer. The role of tofacitinib in the development of lung cancer is uncertain.

Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, breast cancer, melanoma, prostate cancer, and pancreatic cancer. Caution should be used in treating elderly patients, patients who are current or past smokers, and patients with other malignancy risk factors.

Recommendations for NMSC are presented below.

In the controlled phase 3 clinical studies in RA patients, 26 malignancies (excluding NMSC) including 5 lymphomas, were diagnosed in 26 patients receiving tofacitinib / tofacitinib plus DMARD, compared to 0 malignancies (excluding NMSC) in patients in the placebo/placebo plus DMARD group, 2 malignancies in 2 patients in the adalimumab group and 1 in the MTX group. 3800 patients (3942 patient-years of observation) were treated with tofacitinib for durations up to 2 years while 681 patients (203 patient-years of observation) were treated with placebo for a maximum of 6

months and 204 patients (179 patient-years of observation) were treated with adalimumab for 12 months. The exposure-adjusted incidence rate for malignancies and lymphoma was 0.66 and 0.13 events per 100 patient-years, respectively, in the tofacitinib groups.

In the long-term safety population (4867 patients), in RA studies, the rates of malignancies (excluding NMSC) and lymphoma were 0.97 and 0.09 events per 100 patient-years, respectively, consistent with the rate observed in the controlled period.

In a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, an increase in malignancies (excluding NMSC) was observed in patients treated with tofacitinib compared with TNF inhibitor (see Section 4.8 Adverse Effects (Undesirable Effects)). Malignancies (excluding NMSC) were more common in older patients and in patients who were current or past smokers.

Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications (see Section 4.4, Renal Transplant).

Skin Cancer

Melanoma and NMSCs have been reported in patients treated with tofacitinib. NMSCs were also reported in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor. In this study, an increase in overall NMSCs, including cutaneous squamous cell carcinomas was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1). As there is a higher incidence of NMSC in the elderly and in patients with a prior history of NMSC, caution should be used when treating these types of patients. Regular skin examinations are recommended, particularly for patients with an increased risk for, or a prior history of, skin cancer.

Renal Transplant

In studies in renal transplant patients treated with tofacitinib (15 mg twice daily for 3 to 6 months then reduced) and concomitant immunosuppressive agents (induction therapy with basiliximab, high dose corticosteroids, mycophenolic acid products) for prophylaxis of organ rejection, serious infections and Epstein Barr Virus-associated post-transplant lymphoproliferative disorder were observed at an increased rate compared to patients treated with ciclosporin and concomitant immunosuppressive agents.

Tofacitinib Devatis should not be used in combination with potent immunosuppressants because of the possibility of an increased risk of serious infection and post-transplant lymphoproliferative disorder.

Cardiovascular

Tofacitinib causes a decrease in heart rate and a prolongation of the PR interval. Caution should be observed in patients with a low heart rate at baseline (<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischaemic heart disease, or congestive heart failure. Concomitant medications that result in a decrease in heart rate and/or PR interval prolongation should be avoided to the extent possible during treatment with Tofacitinib Devatis (see Section 4.5).

Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials including a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 4.8 Adverse Effects (Undesirable Effects)). The role of JAK inhibition in these events is not known. Events were primarily reported as diverticular perforation, peritonitis, abdominal abscess and appendicitis. The incidence rate of gastrointestinal perforation across all studies (phase 1, phase 2, phase 3 and long-term extension) for all treatment groups all doses was 0.11 events per 100 patient-years with tofacitinib therapy. All patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. The relative contribution of these concomitant medications vs. tofacitinib to the development of gastrointestinal perforations is not known.

Tofacitinib Devatis should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Fractures

Fractures have been observed in patients treated with tofacitinib in clinical studies and the post-marketing setting.

In controlled Phase 3 clinical studies in RA patients, during the 0 to 3 months exposure, the incidence rates for fractures for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and placebo were 2.11, 2.56 and 4.43 patients with events per 100 PYs, respectively.

In a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, fractures were observed across tofacitinib and TNF inhibitor treatment groups (see Section 4.8 Adverse Effects (Undesirable Effects)).

Caution should be used in patients with known risk factors for fractures such as elderly patients, female patients and patients with corticosteroid use.

Hypersensitivity

Reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients receiving tofacitinib. Some events were serious. Many of these events occurred in patients that have a history of multiple allergies. If a serious hypersensitivity reaction occurs, promptly discontinue tofacitinib while evaluating the potential cause or causes of the reaction.

Vaccinations

No data are available on the secondary transmission of infection by live vaccines to patients receiving tofacitinib. Live vaccines should not be given concurrently with Tofacitinib Devatis. It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating Tofacitinib Devatis therapy. The interval between live vaccinations and initiation of Tofacitinib Devatis therapy should be in accordance with current vaccination guidelines regarding immunomodulatory agents. Consistent with these guidelines, if live zoster vaccine is administered, it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus. Vaccination should occur at least

2 weeks but preferably 4 weeks before initiating immunomodulatory agents such as Tofacitinib Devatis.

In a controlled clinical trial, the humoral response to concurrent vaccination with influenza and pneumococcal polysaccharide vaccines in patients with RA initiating tofacitinib 10 mg twice daily or placebo was evaluated. A similar percentage of patients achieved a satisfactory humoral response to influenza vaccine (≥4-fold increase in ≥2 of 3 antigens) in the tofacitinib (57%) and placebo (62%) treatment groups. A modest reduction in the percentage of patients who achieved a satisfactory humoral response to pneumococcal polysaccharide vaccine (≥2-fold increase in ≥6 of 12 serotypes) was observed in patients treated with tofacitinib monotherapy (62%) and MTX monotherapy (62%) as compared with placebo (77%), with a greater reduction in the response rate of patients receiving both tofacitinib and MTX (32%). The clinical significance of this is unknown.

A separate vaccine study evaluated the humoral response to concurrent vaccination with influenza and pneumococcal polysaccharide vaccines in patients receiving tofacitinib 10 mg twice daily for a median of approximately 22 months. Greater than 60% of patients treated with tofacitinib (with or without MTX) had satisfactory responses to influenza and pneumococcal vaccines. Consistent with the controlled trial, patients receiving both tofacitinib and MTX had a lower response rate to pneumococcal polysaccharide vaccine as compared with tofacitinib monotherapy (66% vs. 89%).

A controlled study in patients with RA on background MTX evaluated the humoral and cell mediated responses to immunisation with a live attenuated virus vaccine indicated for prevention of herpes zoster. The immunisation occurred 2 to 3 weeks before initiating a 12-week treatment with tofacitinib 5 mg twice daily or placebo. Six weeks after immunisation with the zoster vaccine, tofacitinib and placebo recipients exhibited similar humoral and cell mediated responses (mean fold change of varicella zoster virus [VZV] Immunoglobulin G [IgG] antibodies 2.11 in tofacitinib 5 mg twice daily and 1.74 in placebo twice daily; VZV IgG fold-rise ≥ 1.5 in 57% of tofacitinib recipients and in 43% of placebo recipients; mean fold change of VZV T-cell Enzyme-Linked ImmunoSpot (ELISPOT) Spot Forming Cells 1.5 in tofacitinib 5 mg twice daily and 1.29 in placebo twice daily). These responses were similar to those observed in healthy volunteers aged 50 years and older.

In this study, one patient experienced dissemination of the vaccine strain of VZV, 16 days after vaccination and 2 days after initiation of tofacitinib. The patient was varicella virus naïve, as evidenced by no previous history of varicella infection and no anti-varicella antibodies at baseline. Tofacitinib was discontinued and the subject recovered after treatment with standard doses of antiviral medication. Subsequent testing showed that this patient made robust anti-varicella T-cell and antibody responses to the vaccine approximately 6 weeks post-vaccination, but not at 2 weeks post-vaccination, as expected for a primary infection.

Interstitial Lung Disease

Events of interstitial lung disease (ILD), some of which had a fatal outcome, have been reported in clinical trials with tofacitinib in RA patients, and in the post-marketing setting, although the role of JAK inhibition in these events is not known. All patients who developed ILD in clinical trials were taking concomitant MTX, corticosteroids and/or sulfasalazine, which have been associated with ILD. Asian patients had an increased risk of ILD (see Section 4.4, Asian Patients).

Tofacitinib Devatis should be used with caution in patients with a risk or history of ILD.

Asian Patients

Asian patients had higher rates of herpes zoster, opportunistic infections, interstitial lung disease, elevated transaminases (alanine aminotransferase (ALT), aspartate aminotransferase (AST)) and decreased white blood cell counts (WBCs). Therefore, Tofacitinib Devatis should be used with caution in Asian patients.

Paediatric Use

The safety and efficacy of tofacitinib in children aged from neonates to <18 years of age has not yet been established.

Use in the Elderly

As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly (see Section 4.8).

Use in Renal Impairment

No dose adjustment is required in patients with mild (creatinine clearance 51-80 mL/min) renal impairment. Tofacitinib Devatis dose should be reduced to 5 mg once daily in patients with moderate (creatinine clearance 30-50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment (including but not limited to those with severe renal impairment who are undergoing haemodialysis) (see Section 4.2 and Section 5.2).

In clinical trials, tofacitinib was not evaluated in patients with baseline creatinine clearance values (estimated by Cockroft-Gault equation) <40 mL/min.

Use in Hepatic Impairment

Subjects with moderate hepatic impairment had 65% higher AUC compared with healthy subjects (see Section 5.2). Tofacitinib has not been studied in patients with severe hepatic impairment, or in patients with positive hepatitis B virus or hepatitis C virus serology. No dose adjustment is required in patients with mild hepatic impairment. Tofacitinib Devatis dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment (see Section 4.2). Tofacitinib Devatis should not be used in patients with severe hepatic impairment (see Section 4.3).

Effects on Laboratory Tests

Lymphocytes

Treatment with tofacitinib was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts below the baseline of approximately 10% during 12 months of therapy (see Section 5.1).

Lymphocyte counts <0.5 x 10^9 cells/L were associated with an increased incidence of treated and serious infections. Avoid initiation of Tofacitinib Devatis treatment in patients with a low lymphocyte count (i.e., <0.5 x 10^9 cells/L). In patients who develop a confirmed absolute lymphocyte count <0.5 x 10^9 cells/L treatment with Tofacitinib Devatis is not recommended. Lymphocytes should be monitored at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts see Section 4.2.

Neutrophils

Treatment with tofacitinib was associated with an increased incidence of neutropenia (<2.0 x 10^9 cells/L) compared to placebo.

Avoid initiation of Tofacitinib Devatis treatment in patients with a low neutrophil count (i.e., <1.0 x 10^9 cells/L). For patients who develop a persistent ANC of 0.5-1.0 x 10^9 cells/L, interrupt Tofacitinib Devatis dosing until ANC is >1.0 x 10^9 cells/L. In patients who develop a confirmed ANC <0.5 x 10^9 cells/L treatment with Tofacitinib Devatis is not recommended. Neutrophils should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter (see Section 4.2 and Section 4.8).

Haemoglobin

Avoid initiation of Tofacitinib Devatis treatment in patients with low haemoglobin values (i.e., <90 g/L). Treatment with Tofacitinib Devatis should be interrupted in patients who develop haemoglobin levels <80 g/L or whose haemoglobin level drops >20 g/L on treatment. Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter (see Section 4.2).

Lipids

Treatment with tofacitinib was associated with dose-dependent increases in lipid parameters such as total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (see Section 4.8). Maximum effects were generally observed within 6 weeks. There were no clinically relevant changes in LDL/HDL cholesterol ratios. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been established.

Increases of total cholesterol, LDL cholesterol, and HDL cholesterol were also reported in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 4.8).

Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of Tofacitinib Devatis therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia. Increases in total and LDL cholesterol associated with Tofacitinib Devatis may be decreased to pre-treatment levels with statin therapy.

Liver Enzyme Elevations

Treatment with tofacitinib was associated with an increased incidence of liver enzyme elevation compared to placebo (see Section 4.8). Most of these abnormalities occurred in studies with background DMARD (primarily MTX) therapy.

Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, Tofacitinib Devatis administration should be interrupted until this diagnosis has been excluded.

Elevations of ALT and AST were reported in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 4.8).

4.5 Interaction with Other Medicines and Other Forms of Interaction

The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19.

Potential for Other Medicines to Influence the Pharmacokinetics of Tofacitinib

Tofacitinib exposure is increased when co-administered with potent inhibitors of CYP3A4 (e.g., ketoconazole) or when administration of one or more concomitant medications results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole). Tofacitinib exposure is decreased when co-administered with potent CYP3A4 inducers (e.g., rifampicin). Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to significantly alter the pharmacokinetics (PK) of tofacitinib.

Methotrexate

Concomitant administration with MTX (15-25 mg MTX once weekly) had no effect on the PK of tofacitinib.

Ketoconazole

Co-administration of ketoconazole, a strong CYP3A4 inhibitor, with a single dose of tofacitinib increased the AUC and C_{max} of tofacitinib by 103% and 16%, respectively (see Section 4.2).

Fluconazole

Co-administration of fluconazole, a moderate inhibitor of CYP3A4 and a strong inhibitor of CYP2C19, increased the AUC and C_{max} of tofacitinib by 79% and 27%, respectively (see Section 4.2).

Ciclosporin

Co-administration of ciclosporin, a moderate inhibitor of CYP3A4, increased the AUC of tofacitinib by 73% and decreased C_{max} of tofacitinib by 17%. The combined use of multiple-dose tofacitinib with this potent immunosuppressive has not been studied in patients with RA and is contraindicated.

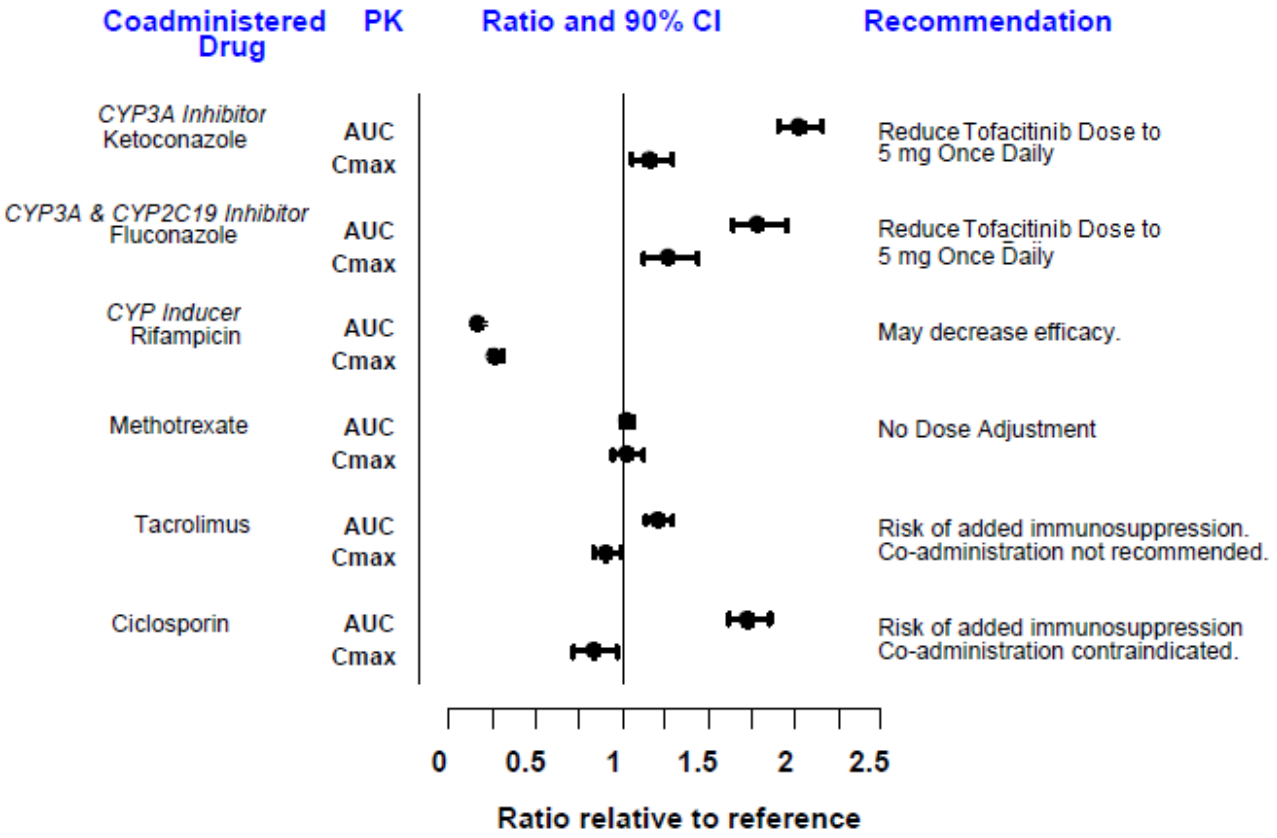
Tacrolimus

Co-administration of tacrolimus, a mild inhibitor of CYP3A4, increased the AUC of tofacitinib by 21% and decreased the C_{max} of tofacitinib by 9%. The combined use of multiple-dose tofacitinib with this potent immunosuppressive has not been studied in patients with RA and is not recommended.

Rifampicin

Co-administration of rifampicin, a strong CYP3A4 inducer, decreased the AUC and C_{max} of tofacitinib by 84% and 74%, respectively (see Section 4.2).

Figure 1. Impact of Other Medicines on the Pharmacokinetics of Tofacitinib



Potential for Tofacitinib to Influence the Pharmacokinetics of Other Medicines

In vitro studies indicate that tofacitinib does not significantly inhibit or induce the activity of the major human drug-metabolising CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations exceeding 80 times the steady state C_{max} of a 5 mg twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the PK of midazolam, a highly sensitive CYP3A4 substrate, when co-administered with tofacitinib.

In RA patients, the oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalise CYP enzyme activity in RA patients. Therefore, co-administration with tofacitinib is not expected to result in clinically relevant increases in the metabolism of CYP substrates in RA patients.

In vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug-metabolising uridine 5'-diphospho-glucuronosyltransferases (UGTs), [UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7] at concentrations exceeding 250 times the steady state C_{max} of a 5 mg twice daily dose.

In vitro data indicate that the potential for tofacitinib to inhibit transporters such as P-glycoprotein, organic anion transporting polypeptide, organic anionic or cationic transporters at therapeutic concentrations is also low.

Oral Contraceptives

Co-administration of tofacitinib did not have an effect on the PK of oral contraceptives, levonorgestrel and ethinyloestradiol, in healthy female volunteers.

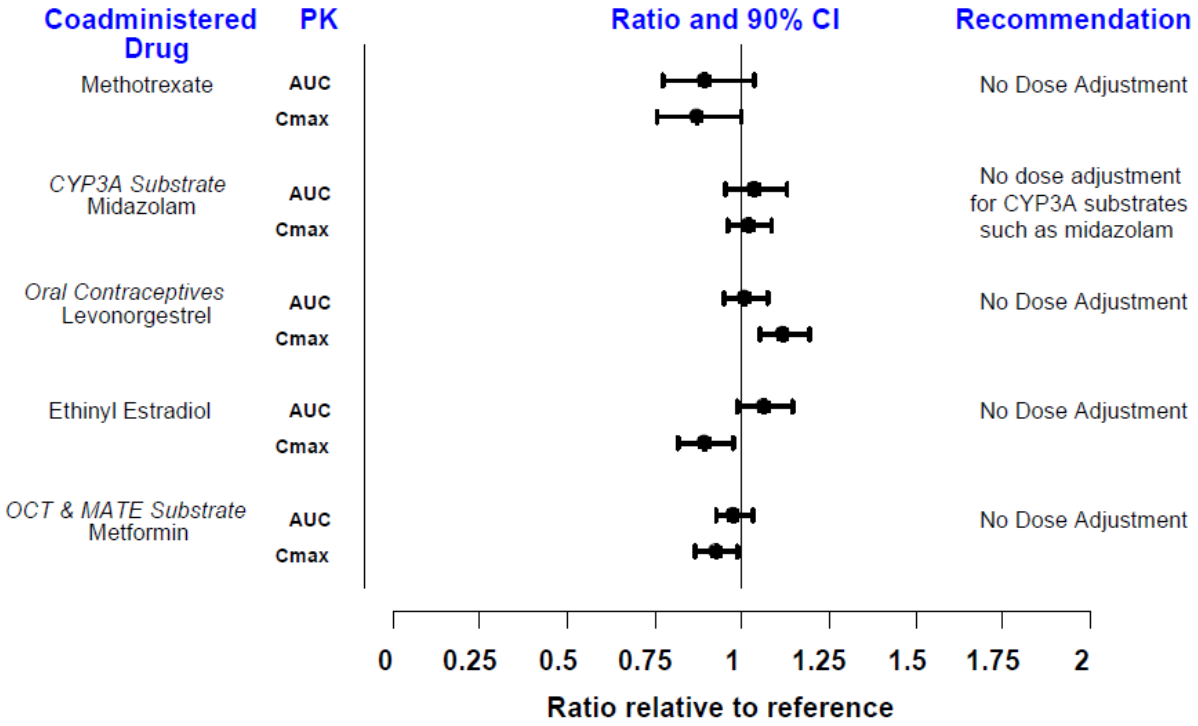
Methotrexate

Co-administration of tofacitinib with MTX 15-25 mg once weekly decreased the AUC and C_{max} of MTX by 10% and 13% respectively. The extent of decrease in MTX exposure does not warrant modifications to the individualised dosing of MTX.

Metformin

Co-administration of tofacitinib did not have an effect on the PK of metformin, indicating that tofacitinib does not interfere with the organic cationic transporter (OCT2) in healthy volunteers.

Figure 2. Impact of Tofacitinib on the Pharmacokinetics of Other Medicines



Medicines that Decrease Heart Rate (HR) and/or Prolong the PR Interval

Tofacitinib results in a decrease in heart rate and an increase in the PR interval (see Section 4.4, Cardiovascular). Caution should be observed if Tofacitinib Devatis is used concomitantly with medicines that lower heart rate and/or prolong the PR interval, such as antiarrhythmics, beta-blockers, alpha2 adrenoceptor agonists, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, and some HIV protease inhibitors.

Combination with Other Therapies

Tofacitinib has not been studied and must not be used in RA patients in combination with biological DMARDs (such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators) and potent immunosuppressants (such as azathioprine and ciclosporin) because of the possibility of increased immunosuppression and increased risk of infection (see Section 4.3).

4.6 Fertility, Pregnancy and Lactation

Pregnancy - Category D

There are no adequate and well-controlled studies on the use of tofacitinib in pregnant women. Tofacitinib has been shown to be teratogenic in rats and rabbits, and to have effects in rats on parturition, and peri/postnatal development.

In an embryo-fetal development (EFD) study in rats given 30, 100, or 300 mg/kg/day, maternal toxicity was observed at doses ≥100 mg/kg/day. Observations included postimplantation loss, consisting of early and late resorptions and consequently a reduced number of viable fetuses, and decreased uterine weight. Fetal developmental effects were observed at 100 mg/kg/day (≥200 times the unbound drug human AUC at 5 mg twice daily). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively, and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). The no observed adverse effect level (NOAEL) for maternal and developmental toxicity in this study was 30 mg/kg/day, a dose at which the unbound drug AUC was ~81-fold the human AUC at 5 mg twice daily.

In an EFD study in rabbits given 10, 30, or 100 mg/kg/day, maternal toxicity was not observed. Fetal developmental effects were observed at ≥30 mg/kg/day. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. The NOAELs for maternal and developmental toxicity in this study were 100 and 10 mg/kg/day, doses at which the total drug AUCs were ~63- and 3-fold, respectively, the human AUC at 5 mg twice daily.

In a perinatal/postnatal rat study, there were reductions in live litter size, postnatal survival, and pup body weights at 50 mg/kg/day (~100 times the unbound exposure in humans at 5 mg twice daily, based on extrapolation from values from other rat studies). At 10 mg/kg/day (~20 times the unbound exposure in humans at 5 mg twice daily, based on extrapolation from values from other rat studies), no effect occurred on sexual maturation or the ability of the F1 generation rats to learn, mate, and produce viable F2 generation fetuses.

In the Phase 2, Phase 3 and long-term extension studies in RA patients, 14 maternal pregnancies were reported in patients treated with tofacitinib. Pregnancy outcomes comprised full-term normal newborn (6 cases), spontaneous abortion (3), elective termination (2), lost to follow-up (2) and low birth weight (1). A spontaneous abortion occurred in the only maternal pregnancy in patients treated with placebo.

Tofacitinib Devatis should not be used during pregnancy or by women attempting to become pregnant. Women of reproductive potential should be advised to use effective contraception both during treatment with Tofacitinib Devatis and for at least 4 weeks after the last dose.

Breastfeeding

Tofacitinib was secreted in the milk of lactating rats. It is not known whether tofacitinib is secreted in human milk. Women should not breastfeed while being treated with Tofacitinib Devatis.

Fertility

In rats, tofacitinib had no effects on male fertility, sperm motility, or sperm concentration at doses up to 100 mg/kg/day (>100 times the human unbound drug AUC at 5 mg twice daily; extrapolated from values from other rat studies). Treatment-related effects on female fertility were noted at ≥10 mg/kg/day in rats (>20 times the human unbound AUC at 5 mg twice daily; based on extrapolation from values from other rat studies).

4.7 Effects on Ability to Drive and Use Machines

No formal studies have been conducted on effects on the ability to drive and use machines.

4.8 Undesirable Effects

The following data include 6 double-blind, controlled, multicentre studies of varying durations from 6 to 24 months (Studies I to VI, see Section 5.1 Clinical Trials). In these studies, 3200 patients were randomised and treated with doses of tofacitinib 5 mg twice daily (616 patients) or 10 mg twice daily (642 patients) monotherapy and tofacitinib 5 mg twice daily (973 patients) or 10 mg twice daily (969 patients) in combination with DMARDs (including MTX).

All patients in these studies had moderate to severe RA. The tofacitinib study population had a mean age of 52 years and 83% were female. The highest proportions of patients in the clinical studies were either White (62%) or Asian (24%).

The long-term safety population includes all patients who participated in a double-blind, controlled study (including earlier development phase studies) and then participated in one of two long-term safety studies.

A total of 6194 patients (phase 1, 2, 3, and long-term extension studies) were treated with any dose of tofacitinib with a mean duration of 3 years, with 19,405.8 patient-years of accumulated total drug exposure based on up to 8 years of continuous exposure to tofacitinib.

Safety information is also included for one large (N=4362), randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (CV risk factors defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularisation procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g., nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations), and were on a stable background dose of methotrexate.

Patients were randomised to open-label tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, or a TNF inhibitor (TNF inhibitor was either etanercept 50 mg once weekly or adalimumab 40 mg every other week) in a 1:1:1 ratio. The co-primary endpoints are adjudicated malignancy (excluding NMSC) and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessment of endpoints are blinded. The study is an event-powered study that also requires at least 1500 patients to be followed for 3 years. The study treatment of tofacitinib 10 mg twice daily has been stopped and the patients were switched to 5 mg twice daily because of a dose-dependent signal of PE.

Clinical Trial Experience

The most common category of serious adverse reactions were serious infections (see Section 4.4).

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials (occurring in ≥2% of patients treated with tofacitinib monotherapy or in combination with DMARDs) were headache, upper respiratory tract infections, nasopharyngitis, diarrhoea, nausea and hypertension.
The proportion of patients who discontinued treatment due to any adverse reactions during first 3 months of the double-blind, placebo- or MTX-controlled studies was 3.8% for patients taking tofacitinib and 3.2% for placebo-treated patients. The most common adverse reactions that resulted in discontinuation of tofacitinib were infections. The most common infections resulting in discontinuation of therapy were herpes zoster and pneumonia.

Table 4 below lists the adverse events (regardless of causality) occurring in ≥1% of patients treated with tofacitinib during the double-blind, placebo-controlled portion of the RA studies.

Table 4: Summary of Adverse Events reported by ≥1% of patients treated with tofacitinib (All Causalities) - double-blind, placebo-controlled portion of Phase 3 Studies (up to 3 months)

Body System / Adverse Event	Tofacitinib 5 mg BD (N=1216)	Tofacitinib 10 mg BD (N=1214)	Placebo (N=681)	Adalimumab 40 mg SC q2w (N=204)	MTX (N=186)
Infections and Infestations					
Upper respiratory tract infection	63 (4.0)	55 (3.4)	23 (3.4)	7 (3.4)	4 (2.2)
Nasopharyngitis	50 (3.1)	52 (3.2)	18 (2.6)	7 (3.4)	7 (3.8)
Urinary tract infection	20 (1.3)	32 (2.0)	11 (1.6)	7 (3.4)	4 (2.2)
Bronchitis	14 (1.2)	17 (1.1)	10 (1.5)	4 (2.0)	0
Influenza	12 (0.8)	16 (1.0)	5 (0.7)	2 (1.0)	1 (0.5)
Herpes zoster	8 (0.5)	16 (1.0)	2 (0.3)	0	0
Blood and Lymphatic System Disorders					
Anaemia	19 (1.2)	16 (1.0)	8 (1.2)	0	0
Metabolism and Nutrition Disorders					
Hypercholesterolaemia	15 (0.9)	19 (1.2)	3 (0.4)	1 (0.5)	0
Nervous System Disorders					
Headache	66 (4.2)	62 (3.8)	15 (2.2)	5 (2.5)	6 (3.2)

Body System / Adverse Event	Tofacitinib 5 mg BD (N=1216)	Tofacitinib 10 mg BD (N=1214)	Placebo (N=681)	Adalimumab 40 mg SC q2w (N=204)	MTX (N=186)
Dizziness	16 (1.0)	15 (0.9)	8 (1.2)	3 (1.5)	3 (1.6)
Vascular Disorders					
Hypertension	27 (1.7)	43 (2.7)	7 (1.0)	0	2 (1.1)
Respiratory, Thoracic and Mediastinal Disorders					
Cough	12 (0.8)	17 (1.1)	11 (1.6)	4 (2.0)	0
Gastrointestinal Disorders					
Diarrhoea	52 (3.3)	47 (2.9)	16 (2.3)	2 (1.0)	8 (4.3)
Nausea	44 (2.8)	45 (2.8)	18 (2.6)	3 (1.5)	23 (12.4)
Dyspepsia	25 (1.6)	34 (2.1)	11 (1.6)	3 (1.5)	4 (2.2)
Abdominal pain upper	28 (1.8)	19 (1.2)	5 (0.7)	3 (1.5)	3 (1.6)
Vomiting	26 (1.6)	19 (1.2)	10 (1.5)	0	4 (2.2)
Constipation	21 (1.3)	21 (1.3)	6 (0.9)	2 (1.0)	5 (2.7)
Gastritis	15 (0.9)	21 (1.3)	6 (0.9)	0	2 (1.1)
Abdominal pain	13 (0.8)	21 (1.3)	7 (1.0)	2 (1.0)	0
Gastroenteritis	13 (0.8)	19 (1.2)	5 (0.7)	0	2 (1.1)
Musculoskeletal and Connective Tissue Disorders					
Rheumatoid arthritis	19 (1.2)	8 (0.5)	17 (2.5)	1 (0.5)	1 (0.5)
Back pain	23 (1.4)	27 (1.7)	5 (0.7)	1 (0.5)	1 (0.5)
Arthralgia	16 (1.0)	14 (0.9)	15 (2.2)	4 (2.0)	4 (2.2)
General Disorders and Administration Site Conditions					
Oedema peripheral	16 (1.0)	24 (1.5)	14 (2.1)	3 (1.5)	2 (1.1)
Investigations					
Blood creatine phosphokinase increased	13 (0.8)	41 (2.5)	3 (0.4)	1 (0.5)	1 (0.5)
Alanine aminotransferase increased	20 (1.3)	22 (1.4)	7 (1.0)	1 (0.5)	4 (2.2)
Weight increased	17 (1.1)	21 (1.3)	4 (0.6)	2 (1.0)	2 (1.1)
Skin and Subcutaneous Tissue Disorders					
Alopecia	18 (1.1)	14 (0.9)	4 (0.6)	0	3 (1.6)

Adverse Drug Reactions for Tofacitinib

The Adverse Drug Reactions (ADRs) listed below are from randomised Phase 3 clinical studies for rheumatoid arthritis, plaque psoriasis, psoriatic arthritis and ulcerative colitis, and are presented by System Organ Class (SOC) and frequency categories, defined using the following convention: very common (≥10%); common (≥1% to <10%), uncommon (≥0.1% to <1%) or rare (≥0.01% to <0.1%).

Blood and Lymphatic System Disorders
Common: Anaemia.
Uncommon: Leucopenia, lymphopenia, neutropenia.

Gastrointestinal Disorders
Common: Abdominal pain, vomiting, diarrhoea, nausea, gastritis, dyspepsia.

General Disorders and Administration Site Conditions
Common: Pyrexia, peripheral oedema, fatigue.

Hepatobiliary Disorders
Uncommon: Hepatic steatosis.

Infections and Infestations
Common: Pneumonia, influenza, herpes zoster, urinary tract infection, sinusitis, bronchitis, nasopharyngitis, pharyngitis.

Uncommon: Tuberculosis, diverticulitis, pyelonephritis, cellulitis, herpes simplex, gastroenteritis viral, viral infection.

Rare: Sepsis, tuberculosis of central nervous system[a], meningitis cryptococcal[a], urosepsis[a], disseminated tuberculosis, necrotising fasciitis[a], bacteraemia[a], staphylococcal bacteraemia[a], *Pneumocystis jiroveci* pneumonia, pneumonia pneumococcal[a], pneumonia bacterial, encephalitis[a], atypical mycobacterial infection[a], *Mycobacterium avium* complex infection[a], cytomegalovirus infection, bacterial arthritis.

Injury, Poisoning and Procedural Complications
*Uncommon: L*igament sprain, muscle strain

Investigations
Common: Gamma glutamyltransferase increased, blood cholesterol increased, weight increased, blood creatine phosphokinase increased.

Uncommon: Hepatic enzyme increased, transaminases increased, liver function test abnormal, blood creatinine increased, low density lipoprotein increased.

Metabolism and Nutrition Disorders
Common: Hyperlipidaemia.
Uncommon: Dyslipidaemia, dehydration.

Musculoskeletal and Connective Tissue Disorders
Common: Arthralgia.
Uncommon: Musculoskeletal pain, joint swelling, tendonitis.

Neoplasm Benign, Malignant and Unspecified (Including Cysts and Polyps)
Uncommon: Nonmelanoma skin cancers[b].

Nervous System Disorders
Common: Headache.
Uncommon: Paraesthesia.

Psychiatric Disorders
Uncommon: Insomnia.

Respiratory, Thoracic and Mediastinal Disorders
Common: Cough.
Uncommon: Dyspnoea, sinus congestion.

Skin and Subcutaneous Tissue Disorders
Common: Rash.
Uncommon: Erythema, pruritus.

Vascular Disorders
Common: Hypertension.
Uncommon: Venous thromboembolism[c].

[a] These ADRs have only been reported in open-label long-term extension studies; therefore, the frequency of these ADRs in Phase 3 randomised trials was estimated.
[b] Nonmelanoma skin cancer is not a preferred term. The frequency is determined by combining frequencies for the PT's of basal cell carcinoma and squamous cell carcinoma.
[c] Venous thromboembolism includes pulmonary embolism and deep vein thrombosis.

Overall Infections

In the controlled portion (0-3 months) of the phase 3 monotherapy study I and study VI, the rate of infections in the 5 mg twice daily and 10 mg twice daily tofacitinib monotherapy groups were 16.1% and 17.9%, respectively, compared to 18.9% in the placebo group. In the controlled portion (0-3 months) of the phase 3 studies II to V with background DMARDs, the rates of infections in the 5 mg twice daily and 10 mg twice daily tofacitinib plus DMARD groups were 21.3% and 21.8%, respectively, compared to 18.4% in the placebo plus DMARD group. In the controlled portion (0-6 months) of the phase 3 studies II to IV with background DMARDs, the rates of infections in the 5 mg twice daily and 10 mg twice daily tofacitinib plus DMARD groups were 34.6% and 32.8%, respectively, compared to 21.3% in the placebo plus DMARD group. The most commonly reported infections were upper respiratory tract infections and nasopharyngitis (3.7% and 3.2%, respectively).

The overall rate of infections with tofacitinib in the long-term safety all exposure population (total 4867 patients) was 46.1 patients with events per 100 patient-years (43.8 and 47.2 events for 5 mg and 10 mg twice daily, respectively). For patients (total 1750) on monotherapy, the rates were 48.9 and 41.9 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively. For patients (total 3117) on background DMARDs, the rates were 41.0 and 50.3 events per 100 patient-years for 5 mg and 10 mg twice daily, respectively.

Infections were also reported in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 5.1).

Serious Infections

In the controlled portion (0-3 months) of the phase 3 monotherapy study I and study VI, the rate of serious infections in the 5 mg twice daily tofacitinib monotherapy group was 0.2%. In the 10 mg twice daily tofacitinib monotherapy group, the rate was 0.3% and the rate was 0 for the placebo group.

In the controlled portion (0-3 months) of the phase 3 studies II to V with background DMARDs, the rates of serious infections in the 5 mg twice daily and 10 mg twice daily tofacitinib plus DMARD groups were 0.8% and 0.8%, respectively, compared to 0.4% in the placebo plus DMARD group. In the controlled portion (0-6 months) of the phase 3 studies II to IV with background DMARDs, the

rates of serious infections in the 5 mg twice daily and 10 mg twice daily tofacitinib plus DMARD groups were 1.8% and 1.4%, respectively, compared to 0.5% in the placebo plus DMARD group.

Of the 4271 patients who enrolled in Studies I to VI, a total of 608 RA patients were 65 years of age and older, including 85 patients 75 years and older. The frequency of serious infection among tofacitinib-treated patients 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

In the long-term safety all exposure population comprised of phase 2 and phase 3 clinical trials and long-term extension studies, the overall rates of serious infections were 2.4 and 3.0 patients with events per 100 patient-years in the 5 mg and 10 mg twice daily tofacitinib groups, respectively. The most common serious infections reported with tofacitinib included pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis and diverticulitis. Cases of opportunistic infections have been reported (see Section 4.4).

Serious infections were also reported in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 5.1).

Clinical Experience in Methotrexate-Naïve Rheumatoid Arthritis Patients

Study VI was an active-controlled clinical trial in MTX-naïve RA patients (see Section 5.1, Clinical Efficacy). The safety experience in these patients was consistent with Studies I-V.

Viral Reactivation

In tofacitinib clinical trials, Japanese and Korean patients appear to have a higher rate of herpes zoster than that observed in other populations (see Section 4.4). Events of herpes zoster were reported in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 5.1).

Venous Thromboembolism

Rheumatoid Arthritis

Events of PE and DVT were reported in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 5.1).

Completed rheumatoid arthritis studies

In the 4 to 12 week placebo period of randomised controlled studies of 4 weeks to 24 months duration, the IRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and placebo for PE were 0.00 (0.00, 0.57), 0.00 (0.00, 0.77), and 0.40 (0.01, 2.22) patients with events per 100 patient-years respectively; the IRs (95% CI) for DVT were 0.00 (0.00, 0.57), 0.21 (0.01, 1.16), and 0.40 (0.01, 2.22) patients with events per 100 patient-years respectively.

In the full randomised period of controlled studies of 4 weeks to 24 months duration, the IRs (95% CI) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily for PE were 0.12 (0.02, 0.34) and 0.15 (0.03, 0.44) patients with events per 100 patient-years respectively; the IRs (95% CI) for DVT were 0.15 (0.04, 0.40) and 0.10 (0.01, 0.36) patients with events per 100 patient-years respectively.

In the long-term safety population that includes exposure during completed randomised controlled studies and open label long-term extension studies, the IRs (95% CI) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily for PE were 0.12 (0.06, 0.22) and 0.13 (0.08, 0.21) patients with events per 100 patient-years respectively; the IRs (95% CI) for DVT were 0.17 (0.09, 0.27) and 0.15 (0.09, 0.22) patients with events per 100 patient-years respectively.

Laboratory Parameters

Lymphocytes

In the controlled clinical studies, confirmed decreases in lymphocyte counts below 0.5 x 10^9 cells/L occurred in 0.23% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

In the long-term safety population, confirmed decreases in lymphocyte counts below 0.5 x 10^9 cells/L occurred in 1.3% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. Confirmed lymphocyte counts <0.5 x 10^9 cells/L were associated with an increased incidence of treated and serious infections (see Section 4.4 and Section 4.2).

Neutrophils

In the controlled clinical studies, confirmed decreases in ANC below 1.0 x 10^9 cells/L occurred in 0.08% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. There were no confirmed decreases in ANC below 0.5 x 10^9 cells/L observed in any treatment group. There was no clear relationship between neutropenia and the occurrence of serious infections.

In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical studies (see Section 4.4 and Section 4.2).

Liver Enzyme Tests

Confirmed increases in liver enzymes ≥3x upper limit of normal (ULN) were uncommonly observed. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of tofacitinib, or reduction in tofacitinib dose, resulted in decrease or normalisation of liver enzymes.
In the controlled portion of the phase 3 placebo-controlled monotherapy study (0-3 months) (Study I, see Section 5.1 Clinical Efficacy), ALT elevations ≥ 3x ULN were observed in 1.65%, 0.41%, and 0% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively. In this study, AST elevations ≥ 3x ULN were observed in 1.65%, 0.41% and 0% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the phase 3 active-controlled monotherapy study (0-24 months) (Study VI, see Section 5.1 Clinical Efficacy), ALT elevations ≥ 3x ULN were observed in 7.1%, 3.0%, and 3.0% of patients receiving MTX, tofacitinib 5 mg and 10 mg twice daily, respectively. In this study, AST elevations ≥ 3x ULN were observed in 3.3%, 1.6% and 1.5% of patients receiving MTX, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the controlled portion of the phase 3 studies on background DMARDs (0-3 months) (Studies II-V, see Section 5.1 Clinical Efficacy), ALT elevations ≥ 3x ULN were observed in 0.9%, 1.24% and 1.14% of patients receiving placebo, tofacitinib 5 mg, and 10 mg twice daily, respectively. In these

studies, AST elevations ≥ 3x ULN were observed in 0.72%, 0.52% and 0.31% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively.

Elevations of ALT and AST were reported in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 5.1).

One patient treated with tofacitinib 10 mg twice daily and MTX had possible drug-induced liver injury (DILI). Despite discontinuation of both drugs, 2-3 months later she developed further increases in transaminase levels. The elevated liver tests responded to prednisolone and azathioprine, possibly consistent with autoimmune hepatitis, but DILI cannot be ruled out.

Lipids

Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were first assessed at one month following initiation of tofacitinib in the controlled double-blind clinical trials. Increases were observed at this time point and remained stable thereafter. Changes in lipid parameters from baseline through the end of the study (6-24 months) in the controlled phase 3 clinical studies are summarised below:

- Mean LDL cholesterol increased by 15% in the tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at month 12, and increased by 16% in the tofacitinib 5 mg twice daily arm and 19% in the tofacitinib 10 mg twice daily arm at month 24.
- Mean HDL cholesterol increased by 17% in the tofacitinib 5 mg twice daily arm and 18% in the tofacitinib 10 mg twice daily arm at month 12, and increased by 19% in the tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at month 24.
- Mean LDL cholesterol/HDL cholesterol ratios were essentially unchanged in tofacitinib -treated patients.
- Apolipoprotein B (ApoB)/ApoA1 ratios were essentially unchanged in tofacitinib-treated patients.

Elevations of LDL cholesterol, and HDL cholesterol, were reported in a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 5.1).

In a controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy.

In the long-term safety populations, elevations in the lipid parameters remained consistent with what was seen in the controlled clinical studies.

Serum Creatinine

In the controlled clinical trials, dose-related elevations in serum creatinine were observed with tofacitinib treatment. The mean increase in serum creatinine was <8.84 µmol/L in the 12-month pooled safety analysis; however, with increasing duration of exposure in the long-term extensions, up to 2.4% of patients were discontinued from tofacitinib treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

Post-Marketing Experience

Immune system disorders

Uncommon: Drug hypersensitivity (events such as angioedema and urticaria have been observed). Some events were also observed in clinical trials.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

There is no experience with overdose of tofacitinib. There is no specific antidote for overdose with tofacitinib. Treatment should be symptomatic and supportive. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

Pharmacokinetic data up to and including a single dose of 100 mg in healthy volunteers indicates that more than 95% of the administered dose is expected to be eliminated within 24 hours.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

Tofacitinib is a selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain-containing receptors for several cytokines, including IL-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, proliferation and function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and type I and II interferons. At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling.

Pharmacodynamics

Treatment up to 6 months with tofacitinib was associated with dose-dependent reductions of circulating CD16/56+ natural killer (NK) cells, with estimated maximum reductions occurring at approximately 8-10 weeks after initiation of therapy. These changes generally resolved within 2-6 weeks after discontinuation of treatment. Treatment with tofacitinib was associated with dose-dependent increases in B cell counts. Changes in circulating T-lymphocyte counts and T-lymphocyte

subsets (CD3+, CD4+ and CD8+) were small and inconsistent. The clinical significance of these changes is unknown.

Following long-term treatment (median duration of tofacitinib treatment of approximately 5 years), CD4+ and CD8+ counts showed median reductions of 28% and 27%, respectively, from baseline. In contrast to the observed decrease after short-term dosing, CD16/56+ NK cell counts showed a median increase of 73% from baseline. CD19+ B cell counts showed no further increases after long-term tofacitinib treatment. These changes returned toward baseline after temporary discontinuation of treatment. There was no evidence of an increased risk of serious or opportunistic infections or herpes zoster at low values of CD4+, CD8+ or NK cell counts or high B cell counts.

Changes in total serum IgG, IgM, and IgA levels over 6-month tofacitinib dosing in patients with RA were small, not dose-dependent and similar to those seen on placebo.

After treatment with tofacitinib in patients with RA, rapid decreases in serum C-reactive protein (CRP) were observed and maintained throughout dosing. Changes in CRP observed with tofacitinib treatment do not reverse fully within 2 weeks after discontinuation, indicating a longer duration of pharmacodynamic activity compared to the half-life.

Clinical Safety

In one large randomised open-label PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor and on a stable dose of methotrexate, patients were treated with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily or a TNF inhibitor. Notably, in February 2019, the dose of tofacitinib in the 10 mg twice daily arm of the study was reduced to 5 mg twice daily after it was determined that the frequency of pulmonary embolism was increased in the tofacitinib 10 mg twice daily treatment arm versus the TNF inhibitor. Additionally, all-cause mortality was increased in the tofacitinib 10 mg twice daily treatment arm versus the TNF inhibitor and tofacitinib 5 mg twice daily treatment arms. In the final study data, patients in the tofacitinib 10 mg twice daily treatment arm were analysed in their originally randomised treatment group. Results from final safety data from the study for selected events follow below.

Mortality

The IRs (95% CI) for all-cause mortality for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.50 (0.33, 0.74), 0.80 (0.57, 1.09), 0.65 (0.50, 0.82), and 0.34 (0.20, 0.54) events per 100 patient-years, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.49 (0.81, 2.74), 2.37 (1.34, 4.18), and 1.91 (1.12, 3.27), respectively.

The IRs (95% CI) for deaths associated with infection for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.08 (0.02, 0.20), 0.18 (0.08, 0.35), 0.13 (0.07, 0.22), and 0.06 (0.01, 0.17) events per 100 patient-years, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.30 (0.29, 5.79), 3.10 (0.84, 11.45), and 2.17 (0.62, 7.62), respectively.

The IRs (95% CI) for deaths associated with cardiovascular events for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily

treatment arms), and TNF inhibitor were 0.25 (0.13, 0.43), 0.41 (0.25, 0.63), 0.33 (0.23, 0.46), and 0.20 (0.10, 0.36) events per 100 patient-years, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.26 (0.55, 2.88), 2.05 (0.96, 4.39), and 1.65 (0.81, 3.34), respectively.

The IRs (95% CI) for deaths associated with malignancies for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.10 (0.03, 0.23), 0.00 (0.00, 0.08), 0.05 (0.02, 0.12), and 0.02 (0.00, 0.11) events per 100 patient-years, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 4.88 (0.57, 41.74), 0 (0.00, Inf), and 2.53 (0.30, 21.64), respectively.

The IRs (95% CI) for deaths associated with other causes (excluding infections, cardiovascular events, malignancies) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.08 (0.02, 0.20), 0.21 (0.10, 0.38), 0.14 (0.08, 0.23), and 0.06 (0.01, 0.17) events per 100 patient-years, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.30 (0.29, 5.81), 3.45 (0.95, 12.54), and 2.34 (0.67, 8.16), respectively.

In tofacitinib clinical studies that included 10 mg twice a day, incidence rates for all-cause mortality in patients treated with tofacitinib 10 mg twice a day have not been higher than rates in patients treated with tofacitinib 5 mg twice a day. Mortality rates in patients treated with tofacitinib are similar to those reported for patients with RA, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, polyarticular course juvenile idiopathic arthritis, and ulcerative colitis, treated with biologic therapies.

Infections

The IRs (95% CI) for all infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 41.74 (39.21, 44.39), 48.73 (45.82, 51.77), 45.02 (43.10, 47.01), and 34.24 (32.07, 36.53) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.20 (1.10, 1.31), 1.36 (1.24, 1.49), and 1.28 (1.18, 1.38), respectively.

The IRs (95% CI) for serious infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 2.86 (2.41, 3.37), 3.64 (3.11, 4.23), 3.24 (2.89, 3.62), and 2.44 (2.02, 2.92) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.17 (0.92, 1.50), 1.48 (1.17, 1.87), and 1.32 (1.07, 1.63), respectively.

The IRs (95% CI) for opportunistic infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.76 (0.54, 1.04), 0.91 (0.66, 1.22), 0.84 (0.67, 1.04), and 0.42 (0.26, 0.64) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.82 (1.07, 3.09), 2.17 (1.29, 3.66), and 1.99 (1.23, 3.22), respectively. The majority of the opportunistic infections in the tofacitinib treatment arms were opportunistic herpes zoster infections; a limited number of events with tuberculosis were also reported. Excluding opportunistic herpes zoster infections and

tuberculosis, the IRs (95% CI) for all other opportunistic infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.08 (0.02, 0.20), 0.14 (0.06, 0.30), 0.11 (0.05, 0.20), and 0.06 (0.01, 0.17) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.30 (0.29, 5.82), 2.40 (0.62, 9.29), and 1.84 (0.51, 6.59), respectively.

The IRs (95% CI) for herpes zoster (includes all herpes zoster events) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms) and TNF inhibitor were 3.75 (3.22, 4.34), 3.94 (3.38, 4.57), 3.84 (3.45, 4.26), and 1.18 (0.90, 1.52) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HR (95% CI) for herpes zoster with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 3.17 (2.36, 4.27), 3.33 (2.48, 4.48), and 3.25 (2.46, 4.29), respectively.

Thromboembolism

Venous Thromboembolism

The IRs (95% CI) for VTE for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms) and TNF inhibitor were 0.33 (0.19, 0.53), 0.70 (0.49, 0.99), 0.51 (0.38, 0.67), and 0.20 (0.10, 0.37) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HR (95% CI) for VTE with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.66 (0.76, 3.63), 3.52 (1.74, 7.12), and 2.56 (1.30, 5.05), respectively.

The IRs (95% CI) for PE for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms) and TNF inhibitor were 0.17 (0.08, 0.33), 0.50 (0.32, 0.74), 0.33 (0.23, 0.46), and 0.06 (0.01, 0.17) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HR (95% CI) for PE with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 2.93 (0.79, 10.83), 8.26 (2.49, 27.43), and 5.53 (1.70, 18.02), respectively.

The IRs (95% CI) for DVT for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms) and TNF inhibitor were 0.21 (0.11, 0.38), 0.31 (0.17, 0.51), 0.26 (0.17, 0.38), and 0.14 (0.06, 0.29) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HR (95% CI) for DVT with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.54 (0.60, 3.97), 2.21 (0.90, 5.43), and 1.87 (0.81, 4.30), respectively.

In a post hoc exploratory biomarker analysis within a large randomised PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, occurrences of subsequent VTEs were observed more frequently in tofacitinib-treated patients with D-dimer level ≥2x ULN at 12 months treatment versus those with D-dimer level <2x ULN. This observation was not identified in TNFi-treated patients. Interpretation is limited by the low number of VTE events and restricted D-dimer test availability (only assessed at Baseline, Month 12, and at the end of the study). In patients who did not have a VTE during the study, mean D-dimer levels were significantly reduced at Month 12 relative to Baseline across all treatment arms. However, D-dimer levels ≥2x ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D-dimer testing in this study. Considering the data and the overall

limitations of this post hoc exploratory biomarker analysis, there is limited utility of conducting D-dimer monitoring in the context of risk mitigation for VTE events.

Arterial Thromboembolism

The IRs (95% CI) for arterial thromboembolism (ATE) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms) and TNF inhibitor were 0.92 (0.68, 1.22), 0.94 (0.68, 1.25), 0.93 (0.75, 1.14), and 0.82 (0.59, 1.12) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HR (95% CI) for ATE with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.12 (0.74, 1.70), 1.14 (0.75, 1.74), and 1.13 (0.78, 1.63), respectively.

Major Adverse Cardiovascular Events (MACE), including Myocardial Infarction

MACE includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths excluding fatal pulmonary embolism. The IRs (95% CI) for MACE for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.91 (0.67, 1.21), 1.05 (0.78, 1.38), 0.98 (0.79, 1.19), and 0.73 (0.52, 1.01) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.24 (0.81, 1.91), 1.43 (0.94, 2.18), and 1.33 (0.91, 1.94), respectively.

In the tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib, and TNFi treatment arms, there were a total of 19, 19, 38, and 11 patients with MI events, respectively. Of these totals, the number of patients with fatal MI events was 0, 3, 3, and 3, respectively, whereas the number of patients with non-fatal MI events was 19, 16, 35, and 8, respectively. Therefore, the IRs that follow are for non-fatal MI. The IRs (95% CI) for non-fatal MI for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), 0.35 (0.24, 0.48), and 0.16 (0.07, 0.31) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 2.32 (1.02, 5.30), 2.08 (0.89, 4.86), and 2.20 (1.02, 4.75), respectively.

Malignancies excluding NMSC

The IRs (95% CI) for malignancies excluding NMSC for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 1.13 (0.87, 1.45), 1.13 (0.86, 1.45), 1.13 (0.94, 1.35), and 0.77 (0.55, 1.04) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.47 (1.00, 2.18), 1.48 (1.00, 2.19), and 1.48 (1.04, 2.09), respectively.
The IRs (95% CI) for lymphoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), 0.09 (0.04, 0.17), and 0.02 (0.00, 0.10) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 3.99 (0.45, 35.70), 6.24 (0.75, 51.86), and 5.09 (0.65, 39.78), respectively.

The IRs (95% CI) for lung cancer for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.23 (0.12, 0.40), 0.32 (0.18, 0.51), 0.28 (0.19, 0.39), and 0.13 (0.05, 0.26) patients with events

per 100 patient-years, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.84 (0.74, 4.62), 2.50 (1.04, 6.02), and 2.17 (0.95, 4.93), respectively.

NMSC

The IRs (95% CI) for NMSC for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.61 (0.41, 0.86), 0.69 (0.47, 0.96), 0.64 (0.50, 0.82), and 0.32 (0.18, 0.52) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.90 (1.04, 3.47), 2.16 (1.19, 3.92), and 2.02 (1.17, 3.50), respectively.

The IRs (95% CI) for basal cell carcinoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.37 (0.22, 0.58), 0.33 (0.19, 0.54), 0.35 (0.24, 0.49), and 0.26 (0.14, 0.44) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.43 (0.71, 2.90), 1.28 (0.61, 2.66), and 1.36 (0.72, 2.56), respectively.

The IRs (95% CI) for cutaneous squamous cell carcinoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.29 (0.16, 0.48), 0.45 (0.29, 0.69), 0.37 (0.26, 0.51), and 0.16 (0.07, 0.31) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.82 (0.77, 4.30), 2.86 (1.27, 6.43), and 2.32 (1.08, 4.99), respectively.

Gastrointestinal Perforations

The IRs (95% CI) for gastrointestinal perforations for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.17 (0.08, 0.33), 0.10 (0.03, 0.24), 0.14 (0.08, 0.23), and 0.08 (0.02, 0.20) patients with events per 100 patient-years, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 2.20 (0.68, 7.15), 1.29 (0.35, 4.80), and 1.76 (0.58, 5.34), respectively.

Fractures

The IRs (95% CI) for fractures for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 2.79 (2.34, 3.30), 2.87 (2.40, 3.40), 2.83 (2.50, 3.19) and 2.27 (1.87, 2.74) patients with events per 100 patient-years, respectively. Compared with TNFi, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.23 (0.96, 1.58), 1.26 (0.97, 1.62) and 1.24 (0.99, 1.55), respectively.

Laboratory tests

Liver enzyme tests

The percentages of patients with at least one post-baseline ALT elevation >1x ULN, 3x ULN, and 5x ULN for the tofacitinib 5 mg twice daily treatment arm were 52.83, 6.01, and 1.68, respectively. The percentages for the tofacitinib 10 mg twice daily treatment arm were 54.46, 6.54, and 1.97,

respectively. The percentages for all tofacitinib (combines tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily) were 53.64, 6.27, and 1.82, respectively. The percentages for the TNF inhibitor treatment arm were 43.33, 3.77, and 1.12, respectively.

The percentages of patients with at least one post-baseline AST elevation >1x ULN, 3x ULN, and 5x ULN for the tofacitinib 5 mg twice daily treatment arm were 45.84, 3.21, and 0.98, respectively. The percentages for the tofacitinib 10 mg twice daily treatment arm were 51.58, 4.57, and 1.62, respectively. The percentages for all tofacitinib (combines tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily) were 48.70, 3.89, and 1.30, respectively. The percentages for the TNF inhibitor treatment arm were 37.18, 2.38, and 0.70, respectively.

Lipids

At 12 months, in the tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor treatment arms, the mean percent increase in LDL cholesterol was 13.80, 17.04, and 5.50, respectively. At 24 months, the mean percent increase was 12.71, 18.14, and 3.64, respectively.

At 12 months, in the tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor treatment arms, the mean percent increase in HDL cholesterol was 11.71, 13.63, and 2.82, respectively. At 24 months, the mean percent increase was 11.58, 13.54, and 1.42, respectively.

Clinical Efficacy

The efficacy and safety of tofacitinib were assessed in six randomised, double-blind, controlled, multicentre studies in patients ≥18 years with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 tender and 6 swollen joints at randomisation (4 swollen and tender joints for Study II). Tofacitinib, 5 mg or 10 mg twice daily, was given as monotherapy (Study I) and in combination with csDMARDs (Study II) in patients with an inadequate response to DMARDs. Tofacitinib, 5 mg or 10 mg twice daily was given in combination with MTX in patients with either an inadequate response to MTX (Study III and Study IV) or inadequate response or intolerance to at least one approved TNF-inhibiting biological agent (Study V). Tofacitinib, 5 mg or 10 mg twice daily was also given as monotherapy to MTX-naïve patients (Study VI).

Study I (A3921045/ORAL Solo) was a 6-month monotherapy study in which 610 patients with moderate to severe active RA who had an inadequate response to a DMARD (nonbiological or biological) received tofacitinib 5 mg or 10 mg twice daily or placebo. At the Month 3 visit, all patients randomised to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 mg or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in Health Assessment Questionnaire – Disability Index (HAQ-DI), and rates of Disease Activity Score DAS28-4(ESR)<2.6.

Study II (A3921046/ORAL Sync) was a 12-month study in which 792 patients with moderate to severe active RA who had an inadequate response to a csDMARD received tofacitinib 5 mg or 10 mg twice daily or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or ciclosporin). At the Month 3 visit, nonresponding patients randomised to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 mg or 10 mg twice daily. At the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3 and rates of DAS28-4(ESR)<2.6 at Month 6.

Study III (A3921064/ORAL Standard) was a 12-month study in 717 patients with moderate to severe active RA who had an inadequate response to MTX. Patients received tofacitinib 5 mg or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR)<2.6 at Month 6.

Study IV (A3921044/ORAL Scan) was a 2-year study with a planned analysis at 1 year in which 797 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR)<2.6 at Month 6.

Study V (A3921032/ORAL Step) was a 6-month study in which 399 patients with moderate to severe active RA who had an inadequate response to at least one approved TNF-inhibiting biological agent received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. At the Month 3 visit, all patients randomised to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 mg or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, HAQ-DI, and DAS28-4(ESR)<2.6.

Study VI (A3921069/ORAL Start) was a 2-year monotherapy study with a planned analysis at 1 year in which 956 MTX-naïve patients with moderate to severe active RA received tofacitinib 5 mg or 10 mg twice daily or MTX dose-titrated over 8 weeks from 10 mg to 20 mg weekly. The primary endpoints were mean change from baseline in van der Heijde mTSS at Month 6 and the proportion of patients who achieved an ACR70 response at Month 6.

Clinical Response

The percentages of tofacitinib-treated patients achieving ACR20, ACR50 and ACR70 responses in Studies I, II, III, IV, and V are shown in Table 5. Results are provided for tofacitinib 5 mg twice daily.

In Studies I and V, patients treated with 5 mg twice daily tofacitinib had statistically superior ACR20, ACR50, and ACR70 response rates at Month 3 vs. placebo-treated patients. In Studies II, III and IV, patients treated with 5 mg twice daily tofacitinib had statistically superior ACR20, ACR50, and ACR70 response rates at Months 3 and 6 vs placebo-treated patients (Table 5).

In Study IV, ACR20/50/70 response rates at Month 12 were maintained through Month 24.

In Study VI (Table 5), the difference from MTX in both tofacitinib groups, in achieving ACR20, ACR50 and ACR70 response rates was statistically significant at all timepoints ($p \leq 0.0001$). Tofacitinib, administered as monotherapy in MTX-naïve patients, significantly improved signs and symptoms of RA in comparison to MTX. Efficacy observed with tofacitinib was sustained through Month 24.

In Studies I, II and V, improvement in ACR20 response rate vs. placebo was observed within 2 weeks. In Study III the proportion achieving an ACR20 response at Month 6; change in HAQ-DI at Month 3, and DAS28-4(ESR) <2.6 at Month 6 were 51.5, 47.2 and 28.3%; -0.55, -0.49 and -0.24; and 6.2%, 6.7% and 1.1% for the 5 mg twice daily tofacitinib, adalimumab 40 mg subcutaneously every other week and placebo groups, respectively. For a pre-specified secondary endpoint, the ACR70 response rates at Month 6 for the 5 mg twice daily tofacitinib group was significantly greater than adalimumab (19.9% and 9.1%, respectively).

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race or disease status. Time to onset was rapid (as early as Week 2 in Studies I, II and V) and the magnitude of response continued to improve with duration of treatment. As with the overall ACR response, each of the components of the ACR response was consistently improved from baseline, including: tender and swollen joint counts; patient and physician global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs, or MTX alone, in all studies.

Patients in the Phase 3 studies had a mean Disease Activity Score (DAS28-4(ESR)) of 6.1–6.7 at baseline. Significant reductions in DAS28-4(ESR) from baseline (mean improvement) of 1.8-2.0 were observed in 5 mg tofacitinib-treated patients compared to placebo-treated patients (0.7-1.1) at 3 months. The proportion of patients achieving a DAS28 clinical remission (DAS28-4(ESR)<2.6) in Studies II, III and IV was significantly higher in patients receiving 5 mg tofacitinib (6–9%) compared to placebo (1–3%) patients at 6 months. In Study III, the percentages of patients achieving DAS28-4(ESR)<2.6 were for adalimumab and tofacitinib twice daily at Month 6.

Table 5: Proportion of Patients with an ACR Response

	Percent of Patients											
	Monotherapy in DMARD Inadequate Responders		**DMARD Inadequate Responders**		**MTX Inadequate Responders**			**MTX Inadequate Responders**		**TNF Inhibitor Inadequate Responders**		**Monotherapy in MTX-naive Patients**	
	Study I (SOLO)		**Study II (SYNC)**		**Study III (Standard)**			**Study IV (SCAN)**		**Study V (STEP)**		**Study VI (START)**	
Response Rate	Placebo N=120	Tofacitinib 5 mg Twice Daily N=241	Placebo + DMARD N=157	Tofacitinib 5 mg Twice Daily + DMARD N=311	Placebo + MTX N=106	Tofacitinib 5 mg Twice Daily + MTX N=196	Adalimumab 40 mg q2 Weeks + MTX N=199	Placebo + MTX N=154	Tofacitinib 5 mg Twice Daily + MTX N=309	Placebo + MTX N=131	Tofacitinib 5 mg Twice Daily + MTX N=132	MTX N=184	Tofacitinib 5 mg Twice Daily N=369
ACR20													
Month 3	27%	60%***	27%	56%***	26%	61%***	56%***	27%	56%***	24%	42%*	52%	70%***
Month 6	NA	69%	31%	53%***	28%	52%***	47%**	25%	51%***	NA	52%	51%	71%***
Month 12	NA	NA	NA	51%	NA	49%	49%	NA	49%	NA	NA	51%	68%***
Month 24	NA	NA	NA	NA	NA	NA	NA	NA	41%	NA	NA	42%	64%***
ACR50													
Month 3	13%	31%***	10%	27%***	7%	34%***	24%***	8%	29%***	8%	27%***	20%	40%***
Month 6	NA	42%	13%	34%***	12%	37%***	28%**	8%	32%***	NA	37%	27%	47%***
Month 12	NA	NA	NA	33%	NA	37%	34%	NA	32%	NA	NA	34%	50%**
Month 24	NA	NA	NA	NA	NA	NA	NA	NA	29%	NA	NA	28%	49%***
ACR70													
Month 3	6%	15%*	2%	8%**	2%	12%**	9%*	3%	11%**	2%	14%**	5%	20%***
Month 6	NA	22%	3%	13%***	2%	20%***	9%*	1%	15%***	NA	16%	12%	25%***
Month 12	NA	NA	NA	19%	NA	23%	17%	NA	19%	NA	NA	15%	29%***
Month 24	NA	NA	NA	NA	NA	NA	NA	NA	17%	NA	NA	15%	34%***

* *p<0.05*, tofacitinib *vs. placebo/MTX*
** *p<0.001*, tofacitinib *vs. placebo/MTX*
*** *p<0.0001*, tofacitinib *vs. placebo/MTX*

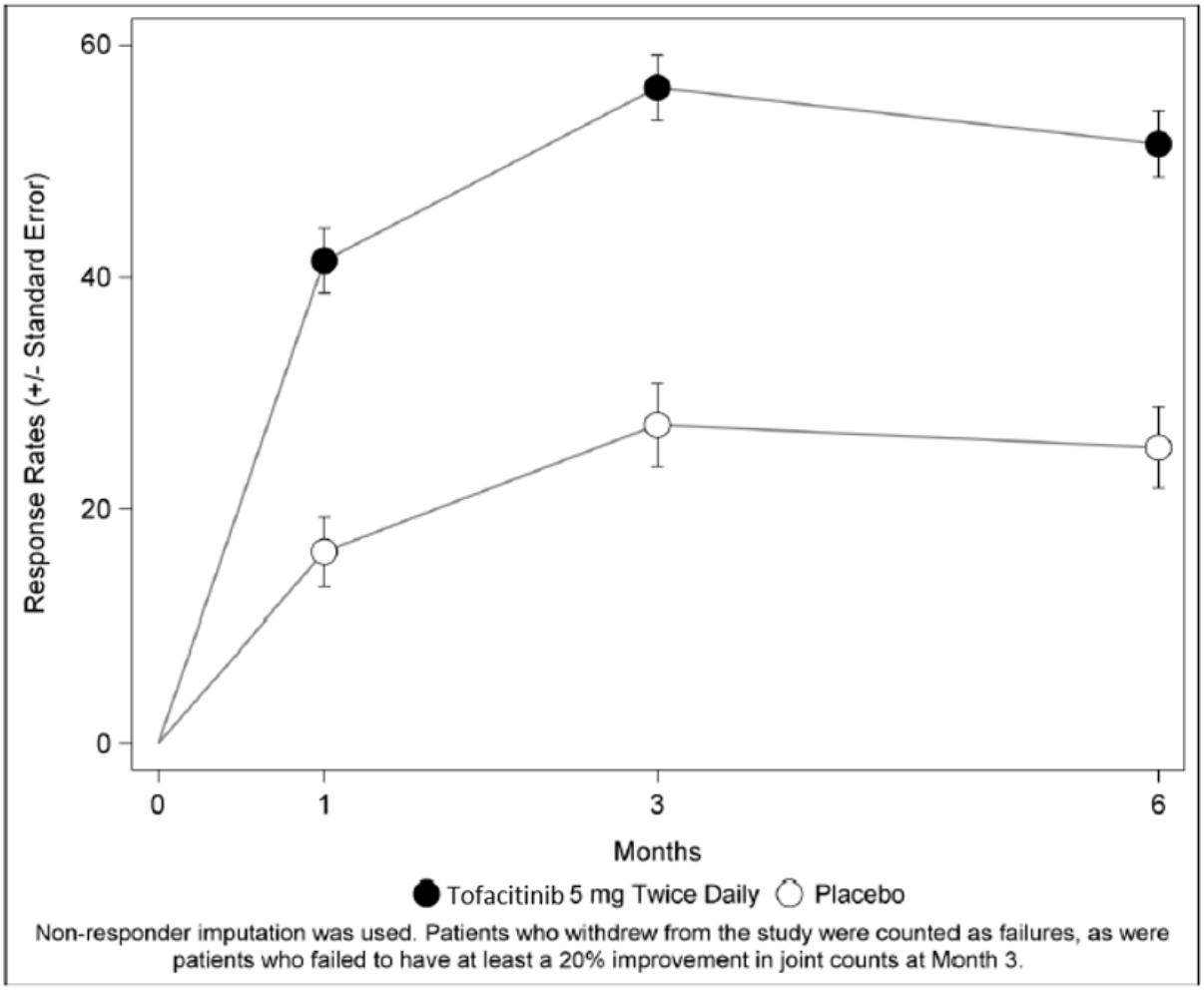
The results of the components of the ACR response criteria for Studies IV and V are shown in Table 6. Similar results were observed in Studies I, II and III.

Table 6: Components of ACR Response at Month 3

	Study IV (SCAN) MTX Inadequate Responders				**Study V (STEP) TNF Inhibitor Inadequate Responders**			
	Tofacitinib 5 mg Twice Daily + MTX N=316		**Placebo + MTX N=156**		**Tofacitinib 5 mg Twice Daily + MTX N=133**		**Placebo + MTX N=132**	
Component (mean)	Baseline	Month 3	Baseline	Month 3	Baseline	Month 3	Baseline	Month 3
Number of tender joints (0-68)	24	13	23	18	28	16	28	21
Number of swollen joints (0-66)	14	6	14	10	16	8	17	12
Pain[a]	58	35	55	47	66	39	61	53
Patient global assessment[a]	58	35	54	47	65	41.2	62	53
Disability index (HAQ-DI)[b]	1.41	1.00	1.31	1.19	1.60	1.20	1.63	1.44
Physician global assessment[a]	59	30	56	43	65	35	64	44
CRP (mg/L)	15.5	6.9	13.7	14.6	19.3	6.2	16.7	18.2

[a] Visual analog scale: 0 = best, 100 = worst
[b] Health Assessment Questionnaire Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities

Figure 3: Percentage of ACR20 Responders by Visit for Study IV



Improvement in physical functioning was measured by the HAQ-DI. Patients receiving tofacitinib 5 mg twice daily demonstrated significantly greater improvement from baseline in physical functioning compared to placebo at Month 3 (Studies I, II, III, and V) and Month 6 (Studies II and III). Tofacitinib 5 mg twice daily treated patients exhibited significantly greater improved physical functioning compared to placebo as early as Week 2 in Studies I and II. Compared with adalimumab-treated patients, at Month 3, patients in the tofacitinib 5 mg twice daily group had similar decreases from baseline in HAQ-DI values. The mean change in HAQ-DI from baseline to Month 3 in Studies I to V are shown in Table 7.

Table 7: Mean Change from Baseline in HAQ-DI

Study I: DMARD Inadequate Responders			
Time	Placebo N=109	Tofacitinib 5 mg monotherapy Twice Daily N=237	
LS Mean Change in HAQ-DI at Month 3[a]	-0.19	-0.50**	
Study II: DMARD Inadequate Responders			
	Placebo + DMARD/s N=147	Tofacitinib 5 mg Twice Daily + DMARD(s) N=292	
LS Mean Change in HAQ-DI at Month 3[a]	-0.21	-0.46**	
Study III: MTX Inadequate Responders			
	Placebo + MTX N=96	Tofacitinib 5 mg BID + MTX N=185	Adalimumab 40 mg QOW + MTX N=188
LS Mean Change in HAQ-DI at Month 3[a]	-0.24	-0.54**	-0.50**
Study IV: MTX Inadequate Responders			
	Placebo+MTX N=146	Tofacitinib 5 mg Twice Daily + MTX N=294	
LS Mean Change in HAQ-DI at Month 3[a]	-0.15	-0.40[b]	
Study V: TNF Inhibitor Inadequate Responders			
	Placebo N=118	Tofacitinib 5 mg Twice Daily + MTX N=117	
LS Mean Change in HAQ-DI at Month 3[a]	-0.18	-0.43**	
Study VI: MTX-naïve: Monotherapy			
	Placebo+MTX N=171	Tofacitinib 5 mg Twice Daily + MTX N=355	
LS Mean Change in HAQ-DI at Month 3[a]	-0.46	-0.74**	

[a.] Primary efficacy time point.
[b.] Statistical significance could not be declared in Study IV due to step-down procedure.
** p<0.0001, tofacitinib (or adalimumab in Study III) vs. placebo + MTX/DMARD
Results are obtained from a longitudinal linear model with change from baseline as a dependent variable and treatment, baseline, visit, region as fixed effects and patient as random effect.
BID=twice daily, CI = confidence interval, FAS = full analysis set, LS = least squares, N = number of patients, MTX = methotrexate, QOW = every other week, HAQ-DI = Health Assessment Questionnaire Disability Index, DMARDs = disease-modifying anti-rheumatic drugs, TNF= tumour necrosis factor

Health-related quality of life was assessed by the Short Form Health Survey (SF-36) in all 5 studies. Tofacitinib-treated patients exhibited significantly greater improvement from baseline compared to placebo in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the

Mental Component Summary (MCS) at Month 3 in Studies I, IV, and V. In Studies III and IV, mean SF-36 improvements were maintained to 12 months in tofacitinib-treated patients.
Improvement in fatigue was evaluated by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale at Month 3 in all studies. Patients receiving tofacitinib 5 mg twice daily demonstrated significantly greater improvement from baseline in fatigue compared to placebo in all 5 studies. In Studies III and IV, mean FACIT-F improvements were maintained to 12 months in tofacitinib-treated patients.

Improvement in sleep was assessed using the Sleep Problems Index I and II summary scales of the Medical Outcomes Study Sleep (MOS-Sleep) measure at Month 3 in all studies. Patients receiving tofacitinib 5 mg twice daily demonstrated significantly greater improvement from baseline in both scales compared to placebo in Studies II, III, and IV. In Studies III and IV, mean improvements in both scales were maintained to 12 months in tofacitinib-treated patients.

Durability of Clinical Responses

Durability of effect was assessed by ACR20, ACR50, ACR70 response rates, mean HAQ-DI, and mean DAS28-4(ESR) in the three Phase 3 DMARD IR studies with duration of at least one year (studies II, III and IV). Efficacy was maintained through to the end of the studies. Evidence of persistence of efficacy with tofacitinib treatment for up to 6 years is also provided from data in a large randomised PASS in RA patients 50 years and older with at least one additional CV risk factor, as well as in open-label, long-term follow-up studies.

5.2 Pharmacokinetic Properties

The PK profile of tofacitinib is characterised by rapid absorption (peak plasma concentrations are reached within 0.5-1 hour), rapid elimination (half-life of ~3 hours) and dose-proportional increases in systemic exposure. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after twice daily administration.

Absorption

Tofacitinib is well-absorbed, with an oral bioavailability of 74%. Co-administration of tofacitinib with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. In clinical trials, tofacitinib was administered without regard to meal.

Distribution

After intravenous administration, the volume of distribution is 87 L. Approximately 40% of circulating tofacitinib is bound to plasma proteins. Tofacitinib binds predominantly to albumin and does not appear to bind to α1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

Metabolism and Excretion

Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged drug, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of tofacitinib is attributed to the parent molecule. *In vitro*, tofacitinib is a substrate for multidrug

resistance (MDR) 1, but not for breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1/1B3, or organic cationic transporter (OCT) 1/2, and is not an inhibitor of MDR1, OATP1B1/1B3, OCT2, organic anion transporter (OAT) 1/3, or multidrug resistance-associated protein (MRP) at clinically meaningful concentrations.

Special Populations

Rheumatoid Arthritis (RA), Elderly (>65 years) patients, Gender, Race

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

Children and Adolescents

The pharmacokinetics, safety and efficacy of tofacitinib in paediatric patients have not been established.

Renal Impairment

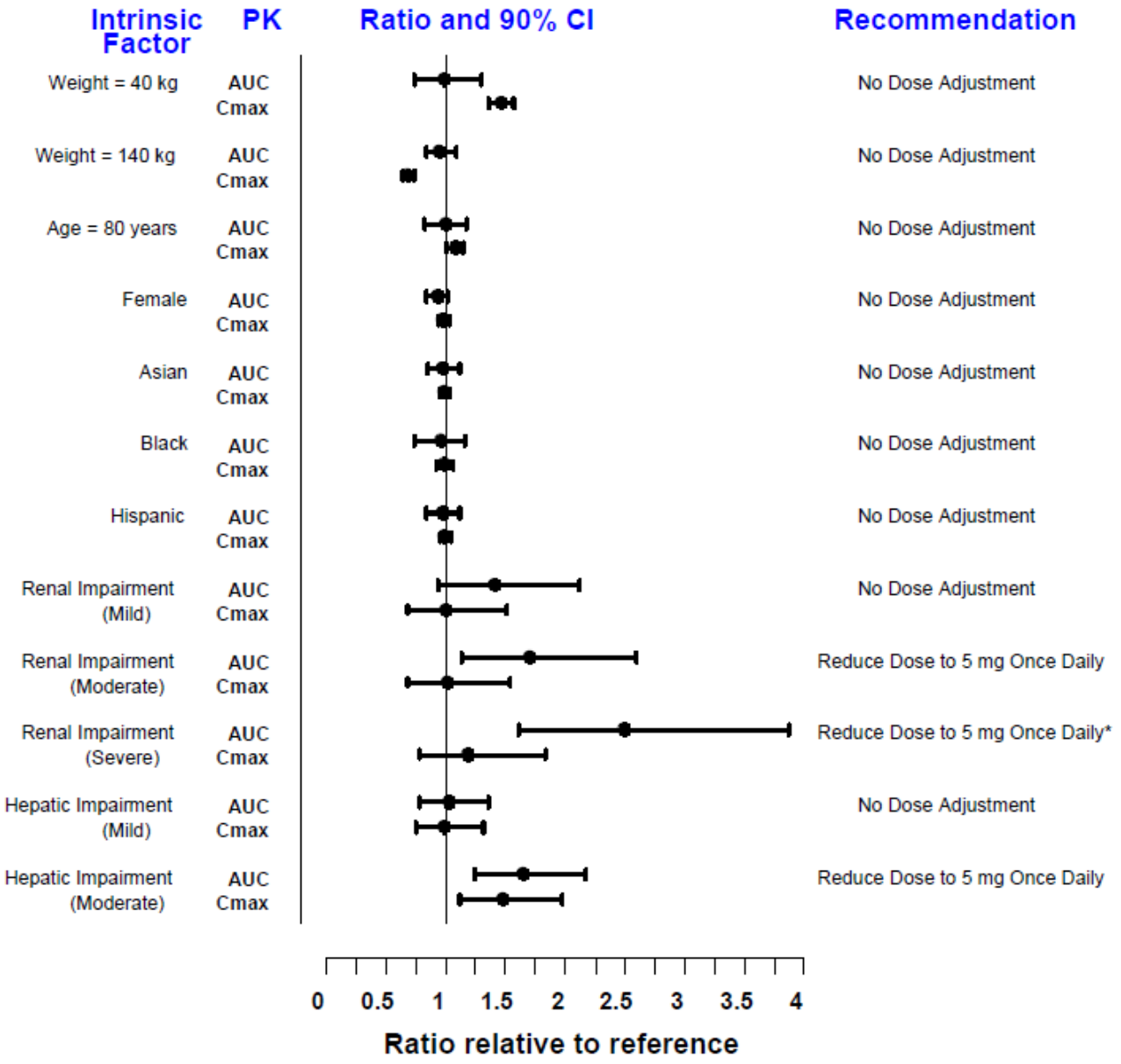
Subjects with mild (creatinine clearance 51-80 mL/min), moderate (30-50 mL/min), and severe (<30 mL/min) renal impairment (estimated GFR (Cockcroft–Gault formula)) had 37%, 43% and 123% higher AUC, respectively, compared with healthy subjects (see Section 4.2). In subjects with end-stage renal disease, the contribution of dialysis to the total clearance of tofacitinib was relatively small.

Hepatic Impairment

Subjects with mild and moderate hepatic impairment had 3%, and 65% higher AUC, respectively, compared with healthy subjects (see Section 4.2 Dose and Method of Administration). Subjects with severe hepatic impairment were not studied. Therefore Tofacitinib Devatis should not be used in patients with severe hepatic impairment (see Section 4.3).

The impact of intrinsic factors on tofacitinib pharmacokinetics is summarised in Figure 4 with dosage adjustment recommendations.

Figure 4: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics



* Supplemental doses are not necessary in patients after dialysis.
** Reference values for weight, age, gender, and race comparisons are 70 kg, 55 years, male and white, respectively; reference groups for renal and hepatic impairment data are subjects with normal renal or hepatic function.

5.3 Preclinical Safety Data

Genotoxicity

Tofacitinib is not mutagenic or genotoxic based on the weight of evidence from a series of *in vitro* and *in vivo* tests for gene mutations and chromosomal aberrations.

Carcinogenicity

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib was not carcinogenic in mice up to a high dose of 200 mg/kg/day (unbound drug AUC of ~38-fold the human AUC at 5 mg twice daily). Benign Leydig cell tumours were observed in rats: benign Leydig cell tumours in rats are not associated with a risk of Leydig cell tumours in humans. Hibernomas (malignancy of brown adipose tissue) were observed in female rats at doses ≥30 mg/kg/day (unbound drug AUC of ~83-fold the human AUC at 5 mg twice daily). Benign thymomas were observed in female rats dosed only at the 100 reduced to 75 mg/kg/day dose (unbound drug AUC of ~187-fold the human AUC at 5 mg twice daily).

Lymphoma was observed in 3 of 8 adult and 0 of 14 juvenile monkeys dosed with tofacitinib at 5 mg/kg twice daily. The NOAEL for the lymphomas was 1 mg/kg twice daily. The unbound AUC at 1 mg/kg twice daily was 341 ng•h/mL, which is similar to the unbound AUC at 5 mg twice daily in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Tablet coating
Hypromellose
Titanium dioxide
Lactose monohydrate
Polyethylene Glycol / Macrogol
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Nature and Contents of Container

Blister packs of PVC/PCTFE sealed with aluminium foil containing 14 or 56 film coated tablets.
HDPE bottles with silica gel desiccant canister and child-resistant polypropylene closure containing 60 film coated tablets.
Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Devatis Limited
Findex, 173 Spey Street, Invercargill 9810,
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Toll Free Number: 0800 887750
www.devatis.nz

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14.11.2024

10. DATE OF REVISION OF THE TEXT

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