TOFACITINIB

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XELJANZ®

5 mg film-coated tablet

XELJANZ® XR

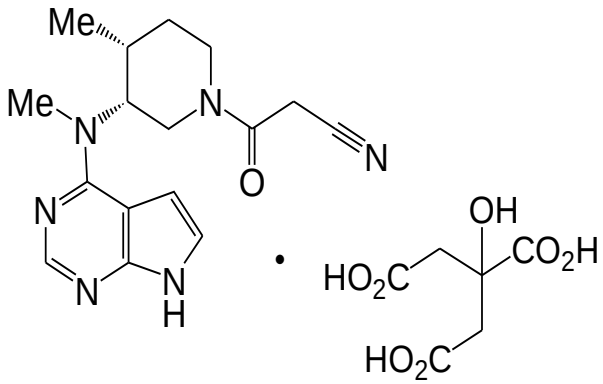
11 mg extended release tablet

1.0 PHARMACOLOGIC CATEGORY

Selective Immunosuppressant

2.0 DESCRIPTION

Tofacitinib citrate (CP-690,550-10) has a molecular weight of 504.5 Daltons, or 312.4 Daltons, for tofacitinib free base (CP-690,550). The molecular formula of Tofacitinib citrate is $C_{16}H_{20}N_6O \bullet C_6H_8O_7$ and its chemical structure is provided below:



Tofacitinib citrate (Xeljanz®) is a white round film-coated tablet with "Pfizer" on one side and "JKI 5" on the other side and is available for oral administration in 5 mg dosage strength.

Tofacitinib citrate (Xeljanz® XR) is pink oval tablet with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet and is available for oral administration in 11 mg dosage strength.

Excipients with known effect:

Each Tofacitinib citrate (Xeljanz®) 5 mg tablet also contains 62.567 mg lactose monohydrate.

Each Tofacitinib citrate (Xeljanz® XR) 11 mg tablet also contains 152.229 mg sorbitol.

For a full list of excipients, see **section 6.1 List of Excipients**.

3.0 FORMULATION/COMPOSITION

Each 5 mg film-coated tablet contains 8.078 mg of Tofacitinib citrate equivalent to 5 mg of tofacitinib free base active pharmaceutical ingredient.

Each 11 mg extended release tablet contains 17.77 mg Tofacitinib citrate equivalent to 11 mg of tofacitinib free base active pharmaceutical ingredient.

4.0 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tofacitinib (Xeljanz®/Xeljanz® XR) are indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).

4.2 Dosage and Method of Administration

Tofacitinib (Xeljanz®/Xeljanz® XR) has not been studied and use should be avoided in combination with TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL23 antagonists, anti-integrins, selective co-stimulation modulators and potent immunosuppressants such as azathioprine, cyclosporine, and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

Tofacitinib (Xeljanz®/Xeljanz® XR) treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

Method of Administration

Tofacitinib (Xeljanz®/Xeljanz® XR) is given orally with or without food.

Swallow Tofacitinib (Xeljanz® XR) tablets whole and intact. Do not crush, split, or chew.

Rheumatoid Arthritis Dosing

Tofacitinib (Xeljanz®/Xeljanz® XR) may be used as monotherapy or in combination with methotrexate (MTX) or other nonbiologic DMARDs.

Tofacitinib (Xeljanz®)

The recommended dose of Tofacitinib (Xeljanz®) is 5 mg administered twice daily.

Tofacitinib (Xeljanz® XR)

The recommended dose of Tofacitinib (Xeljanz® XR) is 11 mg once daily.

Tofacitinib (Xeljanz® XR) 11 mg once daily has demonstrated pharmacokinetic equivalence (AUC and C_{max}) to Tofacitinib (Xeljanz®) 5 mg twice daily.

Switching from Tofacitinib (Xeljanz®) Tablets to Tofacitinib (Xeljanz® XR) Tablets for Rheumatoid Arthritis Dosing

Patients treated with Tofacitinib (Xeljanz®) 5 mg twice daily may be switched to Tofacitinib (Xeljanz® XR) 11 mg once daily the day following the last dose of Tofacitinib (Xeljanz®)

5 mg.

Dose Adjustments in Rheumatoid Arthritis due to Laboratory Abnormalities (see section 4.4 Special Warnings and Precautions for Use)

Dose adjustment or interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia and anemia as described in Tables 1, 2 and 3 below.

It is recommended that Tofacitinib (Xeljanz®/Xeljanz® XR) not be initiated in patients with a lymphocyte count less than 500 cells/mm^3.

Table 1: Dose Adjustments for Lymphopenia

Low Lymphocyte Count (see section 4.4 Special Warnings and Precautions for Use)	
Lab Value (cells/mm^3)	**Recommendation**
Lymphocyte count ≥500	Maintain dose
Lymphocyte count <500 (Confirmed by repeat testing)	Discontinue Tofacitinib (Xeljanz®/Xeljanz® XR)

It is recommended that Tofacitinib (Xeljanz®/Xeljanz® XR) not be initiated in patients with an absolute neutrophil count (ANC) <1000 cells/mm^3.

Table 2: Dose Adjustments for Neutropenia

Low Absolute Neutrophil Count (ANC) (see section 4.4 Special Warnings and Precautions for Use)	
Lab Value (cells/mm^3)	**Recommendation**
ANC >1000	Maintain dose
ANC 500-1000	For persistent decreases in this range, reduce Tofacitinib (Xeljanz®) dose or interrupt Tofacitinib (Xeljanz®/Xeljanz® XR) dosing until ANC is >1000 For patients receiving Tofacitinib (Xeljanz®) 5 mg twice daily, interrupt Tofacitinib (Xeljanz®) dosing. When ANC is >1000, resume Tofacitinib (Xeljanz®) 5 mg twice daily For patients receiving Tofacitinib (Xeljanz®) 11 mg once daily, interrupt Tofacitinib (Xeljanz® XR) dosing. When ANC is >1000, resume Tofacitinib (Xeljanz® XR) 11 mg once daily.
ANC <500 (Confirmed by repeat testing)	Discontinue Tofacitinib (Xeljanz®/Xeljanz® XR)

It is recommended that Tofacitinib (Xeljanz®/Xeljanz® XR) not be initiated in patients with hemoglobin <9 g/dL.

Table 3: Dose Adjustments for Anemia

Low Hemoglobin Value (see section 4.4 Special Warnings and Precautions for Use)	
Lab Value (g/dL)	**Recommendation**
≤2 g/dL decrease and ≥9.0 g/dL	Maintain dose
>2 g/dL decrease or less than 8.0 g/dL (Confirmed by repeat testing)	Interrupt the administration of Tofacitinib (Xeljanz®/Xeljanz® XR) until hemoglobin values have normalized

Special Populations

Renal Impairment

Rheumatoid Arthritis

No dose adjustment is required in patients with mild or moderate renal impairment. Tofacitinib (Xeljanz®) dosage should not exceed 5 mg twice daily, and Tofacitinib (Xeljanz® XR) dosage should not exceed 11 mg once daily, in patients with severe renal impairment (including but not limited to those undergoing hemodialysis) (see **sections 4.4 Special Warnings and Precautions for Use** and **5.2 Pharmacokinetic Properties**).

Hepatic Impairment

Rheumatoid Arthritis

No dose adjustment is required in patients with mild hepatic impairment. Tofacitinib (Xeljanz®/Xeljanz® XR) should not be used in patients with severe hepatic impairment. Tofacitinib (Xeljanz®) dosage should not exceed 5 mg twice daily, and Tofacitinib (Xeljanz® XR) dosage should not exceed 11 mg once daily, in patients with moderate hepatic impairment (see **sections 4.4 Special Warnings and Precautions for Use** and **5.2 Pharmacokinetic Properties**).

Rheumatoid Arthritis Patients Receiving Inhibitors of Cytochrome P450 (CYP3A4) and Cytochrome 2C19 (CYP2C19)

Tofacitinib (Xeljanz®) dosage should not exceed 5 mg twice daily, and Tofacitinib (Xeljanz® XR) dosage should not exceed 11 mg once daily, in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole). Tofacitinib (Xeljanz®) dosage should not exceed 5 mg twice daily, and Tofacitinib (Xeljanz® XR) dosage should not exceed 11 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).

Rheumatoid Arthritis Patients Receiving Inducers of Cytochrome P450 (CYP3A4)

Co-administration of Tofacitinib (Xeljanz®/Xeljanz® XR) with potent CYP inducers (e.g., rifampin) may result in loss of or reduced clinical response (see **section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**). Co-administration of potent inducers of CYP3A4 with Tofacitinib (Xeljanz®/Xeljanz® XR) is not recommended.

Elderly Patients (≥65 years)

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

Pediatric

The safety and efficacy of Tofacitinib (Xeljanz® XR) in children aged from neonates to <18 years of age has not yet been established.

4.3 Contraindications

None

4.4 Special Warnings and Precautions for Use

Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunomodulatory agents, including biologic DMARDs and Tofacitinib (Xeljanz®). The most common serious infections reported with Tofacitinib (Xeljanz®) 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, esophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus infection, BK virus infections, and listeriosis were reported with Tofacitinib (Xeljanz®). Some patients have presented with disseminated rather than localized disease, and rheumatoid arthritis patients were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids which, in addition to rheumatoid arthritis may predispose them to infections. Other serious infections, that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

In one large randomized post-authorization 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 Pharmacodynamic Properties**). Some of these serious infections resulted in death. Opportunistic infections were also reported in the study.

Tofacitinib (Xeljanz®/Xeljanz® XR) should not be initiated in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating Tofacitinib (Xeljanz®/Xeljanz® XR) 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 (Xeljanz®/Xeljanz® XR). Tofacitinib (Xeljanz®/Xeljanz® XR) should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with Tofacitinib (Xeljanz®/Xeljanz® XR), 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 Undesirable Effects**). Caution is also recommended in patients with a history of chronic lung disease as they may be more prone to infections. Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with Tofacitinib (Xeljanz®/Xeljanz® XR), a Janus-kinase (JAK) inhibitor, in clinical trials and in the post-marketing setting although the role of JAK inhibition in these events is not known.

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 Dosage and Method of Administration**.

Tuberculosis

Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of Tofacitinib (Xeljanz®/Xeljanz® XR).

Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering Tofacitinib (Xeljanz®/Xeljanz® XR).

Antituberculosis therapy should also be considered prior to administration of Tofacitinib (Xeljanz®/Xeljanz® XR) 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 (Xeljanz®/Xeljanz® XR). In one large randomized post authorization safety study (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 Pharmacodynamic Properties**). Post-marketing cases of hepatitis B reactivation have been reported in patients treated with Tofacitinib (Xeljanz®). The impact of Tofacitinib (Xeljanz®/Xeljanz® XR) 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.

The risk of herpes zoster appears to be higher in Japanese and Korean patients treated with Tofacitinib (Xeljanz®).

Progressive multifocal leukoencephalopathy (PML) has been reported during post-marketing use of Xeljanz®/Xeljanz® XR, for the treatment of autoimmune diseases (including off-label use). PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological symptoms. If PML is suspected, withhold dosing with Xeljanz®/Xeljanz® XR during appropriate diagnostic evaluation. If PML is confirmed, treatment with Xeljanz®/Xeljanz® XR should be discontinued.

Venous Thromboembolism

Venous thromboembolism (VTE) has been observed in patients taking Tofacitinib (Xeljanz®/Xeljanz® XR) in clinical trials and post-marketing reporting (see Tables 4 and 5 in **section 4.8 Undesirable Effects**). In one large randomized 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 (Xeljanz®) compared to TNF inhibitors (see **section 5.1 Pharmacodynamic Properties**). 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 **sections 4.8 Undesirable Effects** and **5.1 Pharmacodynamic Properties**).

Deep vein thrombosis (DVT) events were observed in all three treatment groups in this study (see **section 5.1 Pharmacodynamic Properties**).

Assess patients for VTE risk factors before starting treatment and periodically during treatment. Use Tofacitinib (Xeljanz®/Xeljanz® XR) with caution in patients 65 years of age and older and in patients in whom VTE risk factors are identified, (e.g., history of thrombosis). 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 randomized 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 Pharmacodynamic Properties**). MACE, including events of myocardial infarction, were more common in patients 65 years of age and older, in patients who were current or past, long-time smokers, and in patients with a history of atherosclerotic cardiovascular disease (ASCVD). Caution should be used in treating patients 65 years of age and older, patients who are current or past, long-time smokers, and patients with other cardiovascular risk factors (e.g., history of ASCVD). In patients with these risk factors, an individualized benefit-risk assessment should

be completed prior to a decision on treatment initiation or continuation (see **section 5.1 Pharmacodynamic Properties**).

Malignancy and Lymphoproliferative Disorder (Excluding Non-melanoma Skin Cancer [NMSC])

Consider the risks and benefits of Tofacitinib (Xeljanz®/Xeljanz® XR) treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing Tofacitinib (Xeljanz®/Xeljanz® XR) in patients who develop a malignancy. The possibility exists for Tofacitinib (Xeljanz®/Xeljanz® XR) to affect host defenses against malignancies.

An increase in malignancies was observed in patients treated with tofacitinib compared to TNF inhibitor in a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see **section 5.1 Pharmacodynamic Properties**). Malignancies excluding NMSC were more common in patients 65 years of age and older, and in patients who were current or past, long-time smokers. Caution should be used in treating patients 65 years of age and older, patients who are current or past, long-time smokers, and patients with other malignancy risk factors (e.g., current malignancy or history of malignancy). In patients with these risk factors, an individualized benefit-risk assessment should be completed prior to a decision on treatment initiation or continuation (see **section 5.1 Pharmacodynamic Properties**).

Lymphomas have been observed in patients treated with Tofacitinib (Xeljanz®/Xeljanz® XR) and in patients treated with Tofacitinib (Xeljanz®) in a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see **section 5.1 Pharmacodynamic Properties**). Patients with rheumatoid arthritis, particularly those with highly active disease, may be at a higher risk (up to several-fold) than the general population for the development of lymphoma. The role of Tofacitinib (Xeljanz®/Xeljanz® XR) in the development of lymphoma is uncertain.

Lung cancers have been observed in patients treated with Tofacitinib (Xeljanz®/Xeljanz® XR). Lung cancers were also observed in patients treated with Tofacitinib (Xeljanz®) in a large randomized 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 (Xeljanz®) 10 mg twice daily compared with TNF inhibitor (see **section 5.1 Pharmacodynamic Properties**). 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 (Xeljanz®/Xeljanz® XR) 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.

The role of treatment with Tofacitinib (Xeljanz®/Xeljanz® XR) on the development and course of malignancies is not known.

Recommendations for non-melanoma skin cancer are presented below.

Rheumatoid Arthritis

In controlled Phase 3 clinical studies in rheumatoid arthritis patients, 26 malignancies (excluding NMSC) including 5 lymphoma were diagnosed in 26 patients receiving Tofacitinib (Xeljanz®/Xeljanz® XR) plus DMARD, compared to 0 malignancies (excluding NMSC) in patients in the placebo/placebo plus DMARD and 2 in 2 patients in the adalimumab group, 1 in 1 patient in the methotrexate group. 3800 patients (3,942 patient-years of observation) were treated with Tofacitinib (Xeljanz®) 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 (Xeljanz®) groups.

In the long-term safety population (4,867 patients), in rheumatoid arthritis studies, the rate of malignancies (excluding NMSC) and lymphoma was 0.97 and 0.09 events per 100 patient-years, respectively consistent with the rate observed in the controlled period.

In a large randomized 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 (Xeljanz®) compared with TNF inhibitor (see **section 5.1 Pharmacodynamic Properties**). Malignancies (excluding NMSC) were more common in patients 65 years of age and older and in patients who were current or past, long-time smokers.

Non-melanoma Skin Cancer

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with Tofacitinib (Xeljanz®/Xeljanz® XR). NMSCs were also reported in a large randomized 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 Pharmacodynamic Properties**). 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. Periodic skin examination is recommended for patients who are at increased risk for skin cancer (see Table 4 in **section 4.8 Undesirable Effects**).

Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials, including a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see **section 5.1 Pharmacodynamic Properties**). The role of JAK inhibition in these events is not known. Events were primarily reported as diverticular perforation, peritonitis, abdominal abscess and appendicitis. In the rheumatoid arthritis clinical trials, the incidence rate of gastrointestinal perforation across all studies (Phase 1, Phase 2, Phase 3 and long-term extension) for all treatments groups all doses was 0.11 events per 100 patient-years with Tofacitinib (Xeljanz®) therapy. Rheumatoid arthritis patients who developed gastrointestinal perforations were taking concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. The relative contribution of these concomitant medications vs. Tofacitinib (Xeljanz®) to the development of gastrointestinal perforations is not known.

Tofacitinib (Xeljanz®/Xeljanz® XR) 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 (Xeljanz®/Xeljanz® XR) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and placebo were 2.11, 2.56 and 4.43 patients with events per 100 PYs, respectively.

In a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, fractures were observed across Tofacitinib (Xeljanz®) and TNF inhibitor treatment groups (see **section 5.1 Pharmacodynamic Properties**).

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 (Xeljanz®/Xeljanz® XR). 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.

Laboratory Parameters

Lymphocytes

Lymphocyte counts <500 cells/mm^3 were associated with an increased incidence of treated and serious infections. It is not recommended to initiate Tofacitinib (Xeljanz®/Xeljanz® XR) treatment in patients with a low lymphocyte count (i.e., <500 cells/mm^3). In patients who develop a confirmed absolute lymphocyte count <500 cells/mm^3 treatment with Tofacitinib (Xeljanz®/Xeljanz® XR) 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 Dosage and Method of Administration**).

Neutrophils

Treatment with Tofacitinib (Xeljanz®) was associated with an increased incidence of neutropenia (<2000 cells/mm^3) compared to placebo. It is not recommended to initiate Tofacitinib (Xeljanz®/Xeljanz® XR) treatment in patients with a low neutrophil count (i.e., ANC <1000 cells/mm^3). For patients taking Tofacitinib (Xeljanz®) 5 mg twice daily or Tofacitinib (Xeljanz® XR) 11 mg once daily who develop a persistent ANC of 500-

1000 cells/mm^3, interrupt Tofacitinib (Xeljanz®/Xeljanz® XR) dosing until ANC is >1000 cells/mm^3. In patients who develop a confirmed absolute neutrophil count <500 cells/mm^3 treatment with Tofacitinib (Xeljanz®/Xeljanz® XR) is not recommended. Neutrophils should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter (see **sections 4.2 Dosage and Method of Administration** and **4.8 Undesirable Effects**).

Hemoglobin

It is not recommended to initiate Tofacitinib (Xeljanz®/Xeljanz® XR) treatment in patients with low hemoglobin values (i.e., <9 g/dL). Treatment with Tofacitinib (Xeljanz®/Xeljanz® XR) should be interrupted in patients who develop hemoglobin levels <8 g/dL or whose hemoglobin level drops >2 g/dL on treatment. Hemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter (see **sections 4.2 Dosage and Method of Administration** and **4.8 Undesirable Effects**).

Lipids

Treatment with Tofacitinib (Xeljanz®) was associated with increases in lipid parameters, such as total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. Increases of total cholesterol, LDL cholesterol, and HDL cholesterol were also reported in a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see **section 5.1 Pharmacodynamic Properties**).

Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of Tofacitinib (Xeljanz®/Xeljanz® XR) therapy. Patients should be managed according to clinical guidelines (e.g., National Cholesterol Educational Program) for the management of hyperlipidemia. Increases in total and LDL cholesterol associated with Tofacitinib (Xeljanz®) may be decreased to pretreatment levels with statin therapy.

Hypoglycemia in Patients Treated for Diabetes

There have been reports of hypoglycemia following initiation of Tofacitinib (Xeljanz®/Xeljanz® XR) in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycemia occurs.

Vaccinations

No data are available on the secondary transmission of infection by live vaccines to patients receiving Tofacitinib (Xeljanz®/Xeljanz® XR). It is recommended that live vaccines not be given concurrently with Tofacitinib (Xeljanz®/Xeljanz® XR). It is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Tofacitinib (Xeljanz®/Xeljanz® XR) therapy. The interval between live vaccinations and initiation of tofacitinib 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.

In a controlled clinical trial, the humoral response to concurrent vaccination with influenza and pneumococcal polysaccharide vaccines in patients with rheumatoid arthritis 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 methotrexate monotherapy (62%) as compared with placebo (77%), with a greater reduction in the response rate of patients receiving both tofacitinib and methotrexate (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 methotrexate) 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 rheumatoid arthritis on background methotrexate evaluated the humoral and cell-mediated responses to immunization with a live-attenuated virus vaccine (Zostavax) indicated for prevention of herpes zoster. The immunization occurred 2 to 3 weeks before initiating a 12-week treatment with tofacitinib 5 mg twice daily or placebo. Six weeks after immunization with the zoster vaccine, tofacitinib and placebo recipients exhibited similar humoral and cell-mediated responses (mean fold change of VZV 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 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 varicella zoster virus, 16 days after vaccination. 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.

Patients with Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Tofacitinib (Xeljanz®) dose should not exceed 5 mg twice daily and Tofacitinib (Xeljanz® XR) dose should not exceed 11 mg once daily in patients with severe renal impairment (see **section 4.2 Dosage and Method of Administration**).

In clinical trials, Tofacitinib (Xeljanz®/Xeljanz® XR) was not evaluated in patients with baseline creatinine clearance values (estimated by Cockcroft-Gault equation) <40 mL/min (see **sections 4.2 Dosage and Method of Administration** and **5.2 Pharmacokinetic Properties**).

Patients with Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment. Tofacitinib (Xeljanz®) dose should not exceed 5 mg twice daily and Tofacitinib (Xeljanz® XR) dose should not exceed 11 mg once daily in patients with moderate hepatic impairment (see **section 4.2 Dosage and Method of Administration**).

Tofacitinib (Xeljanz®/Xeljanz® XR) should not be used in patients with severe hepatic impairment (see **section 4.2 Dosage and Method of Administration**). In clinical trials, Tofacitinib (Xeljanz®/Xeljanz® XR) was not evaluated in patients with severe hepatic impairment, or in patients with positive HBV or HCV serology.

Combination with Other Therapies

Rheumatoid Arthritis

Tofacitinib (Xeljanz®/Xeljanz® XR) has not been studied and its use should be avoided in RA patients in combination with biological DMARDs, such as TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators and potent immunosuppressants, such as azathioprine and cyclosporine because of the possibility of increased immunosuppression and increased risk of infection.

General

Specific to Tofacitinib (Xeljanz® XR)

As with any other non-deformable material, caution should be used when administering Tofacitinib (Xeljanz® XR) to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable modified release formulation.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Interactions Affecting the Use of Tofacitinib (Xeljanz®/Xeljanz® XR)

Since tofacitinib is metabolized by CYP3A4, interaction with drugs that inhibit or induce CYP3A4 is likely. Tofacitinib exposure is increased when co-administered with potent inhibitors of cytochrome P450 (CYP) 3A4 (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) (see **section 4.2 Dosage and Method of Administration**).

Tofacitinib exposure is decreased when co-administered with potent CYP inducers (e.g., rifampin). Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to significantly alter the PK of tofacitinib.

Concomitant administration with methotrexate (15-25 mg MTX once weekly) had no effect on the PK of tofacitinib. Co-administration of ketoconazole, a strong CYP3A4 inhibitor, with a single dose of tofacitinib increased the AUC and C_{max} by 103% and 16%, respectively. 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. Co-administration of tacrolimus (Tac), a mild inhibitor of CYP3A4, increased the AUC of tofacitinib by 21% and decreased the C_{max} of tofacitinib by 9%. Co-administration of cyclosporine (CsA), 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 these potent immunosuppressives has not been studied in patients with rheumatoid arthritis. Co-administration of rifampin, a strong CYP3A4 inducer, decreased the AUC and C_{max} of tofacitinib by 84% and 74%, respectively (see **section 4.2 Dosage and Method of Administration**).

Potential for Tofacitinib (Xeljanz®/Xeljanz® XR) to Influence the PK of Other Drugs

In vitro studies indicate that tofacitinib does not significantly inhibit or induce the activity of the major human drug metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations exceeding 80 times the steady state total C_{max} at 5 mg twice daily dose in rheumatoid arthritis patients. 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 vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug-metabolizing uridine 5'-diphospho-glucuronosyltransferases (UGTs), [UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7] at concentrations exceeding 250 times the steady-state total C_{max} at 5 mg twice daily dose in rheumatoid arthritis patients.

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.

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

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

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.

In rheumatoid arthritis patients, the oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalize 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.

Pediatric Population

Drug-drug interaction studies have only been performed in adults.

4.6 Fertility, Pregnancy and Lactation

There are no adequate and well-controlled studies on the use of Tofacitinib (Xeljanz®/Xeljanz® XR) in pregnant women. Tofacitinib has been shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility, parturition, and peri-/post-natal development (see **section 5.3 Preclinical Safety Data**). Tofacitinib (Xeljanz®/Xeljanz® XR) should not be used during pregnancy unless clearly necessary.

Women of reproductive potential should be advised to use effective contraception during treatment with Tofacitinib (Xeljanz®/Xeljanz® XR) and for at least 4 weeks after the last dose.

Based on published data, tofacitinib is present in human milk. Information on the effects of tofacitinib on the breastfed infant from published literature and post-marketing data is limited to a small number of cases with no causally related adverse events. There are no data on the effects on milk production. Women should not breastfeed while treated with Tofacitinib (Xeljanz®/Xeljanz® XR).

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

Rheumatoid Arthritis

The following data includes 6 double-blind, controlled, multicenter studies of varying durations from 6-24 months (Studies I-VI, see **section 5.1 Pharmacodynamic Properties**). In these studies, 3200 patients were randomized and treated to doses of Tofacitinib (Xeljanz®) 5 mg twice daily (616 patients) or 10 mg twice daily (642 patients) monotherapy and Tofacitinib (Xeljanz®) 5 mg twice daily (973 patients) or 10 mg twice daily (969 patients) in combination with DMARDs (including methotrexate).

All patients in these studies had moderate to severe rheumatoid arthritis. The study Tofacitinib (Xeljanz®) population had a mean age of 52.1 years and 83.2% were female.

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 (Xeljanz®) with a mean duration of 3.13 years, with 19,405.8 patient-years of accumulated total drug exposure based on more than 8 years of continuous exposure to Tofacitinib (Xeljanz®).

Safety information is also included for one large (N=4362), randomized post-authorization safety study (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 revascularization 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. The majority (more than 90%) of tofacitinib patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively.

Patients were randomized 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 Trials Experience

The most common category of serious adverse reactions in rheumatoid arthritis was serious infections (see **section 4.4 Special Warnings and Precautions for Use**).

Rheumatoid Arthritis

In rheumatoid arthritis, the most commonly reported adverse reactions during the first 3 months in controlled clinical trials (occurring in ≥2% of patients treated with Tofacitinib (Xeljanz®) monotherapy or in combination with DMARDs) were headache, upper respiratory tract infections, nasopharyngitis, hypertension, nausea, and diarrhea.

The proportion of patients who discontinued treatment due to any adverse reactions during first 3 months of the double-blind, placebo or methotrexate controlled studies was 3.8% for patients taking Tofacitinib (Xeljanz®) and 3.2% for placebo-treated patients. The most common infections resulting in discontinuation of therapy were herpes zoster and pneumonia.

The Adverse Drug Reactions (ADRs) listed in Tables 4 and 5 below are presented by System Organ Class (SOC) and Council for International Organization of Medical Science (CIOMS) frequency category. Within each SOC, undesirable effects are presented in order of decreasing seriousness or clinical importance.

Table 4. Adverse Drug Reactions by SOC and CIOMS Frequency Categories[a]

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
Infections and infestations	Pneumonia Influenza Herpes zoster Urinary tract infection	Tuberculosis Diverticulitis Pyelonephritis Cellulitis	Sepsis Tuberculosis of central nervous system[b] Meningitis cryptococcal[b]

Table 4. Adverse Drug Reactions by SOC and CIOMS Frequency Categories[a]			
System Organ Class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**
	Sinusitis Bronchitis Nasopharyngitis Pharyngitis	Herpes simplex Gastroenteritis viral Viral infection	Urosepsis Disseminated tuberculosis Necrotizing fasciitis[b] Bacteremia[b] Staphylococcal bacteremia[b] *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal[b] Pneumonia bacterial Encephalitis[b] Atypical mycobacterial infection[b] *Mycobacterium avium* complex infection[b] Cytomegalovirus infection Arthritis bacterial[c]
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Non-melanoma skin cancers[d]	
Blood and lymphatic system disorders	Anemia	Leukopenia Lymphopenia Neutropenia	
Immune system disorders		Drug hypersensitivity[e]	
Metabolism and nutrition disorders	Hyperlipidemia	Dyslipidemia Dehydration	
Psychiatric disorders		Insomnia	
Nervous system disorders	Headache	Paresthesia	
Vascular disorders	Hypertension	Venous thromboembolism[f]	
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnea Sinus congestion	
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhea Nausea Gastritis Dyspepsia		
Hepatobiliary disorders		Hepatic steatosis	
Skin and subcutaneous tissue disorders	Rash Acne[g]	Erythema Pruritus	
Musculoskeletal and connective tissue disorders	Arthralgia	Musculoskeletal pain Joint swelling Tendonitis	
General disorders and administration site conditions	Pyrexia Edema peripheral Fatigue		

Table 4. Adverse Drug Reactions by SOC and CIOMS Frequency Categories[a]			
System Organ Class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**
Investigations	Gamma-glutamyltransferase increased Blood cholesterol increased Weight increased Blood creatine phosphokinase increased	Hepatic enzyme increased Transaminases increased Liver function test abnormal Blood creatinine increased Low density lipoprotein increased	
Injury, poisoning and procedural complications		Ligament sprain Muscle strain	

Abbreviations: ADR=adverse drug reaction; NMSC=Non-melanoma skin cancers; PT=preferred term.

[a] The frequencies are based on pooled Phase 3 randomized clinical trial data (excluding Study A3921133).

[b] The adverse drug reactions have only been reported in open-label long-term extension studies; therefore the frequency of these adverse drug reactions in Phase 3 randomized trials was estimated.

[c] The frequency of arthritis bacterial is determined by combined frequencies for PTs of arthritis bacterial and arthritis infective.

[d] NMSC identified as ADR in 2013; NMSC is not a PT: the frequency is determined by combining frequencies for PTs of basal cell cancer and squamous cell cancer of the skin.

[e] Spontaneous reporting data (events such as angioedema and urticaria have been observed). Some events were also observed in clinical trials.

[f] Venous thromboembolism (e.g., pulmonary embolism, deep vein thrombosis, retinal venous thrombosis, cerebral venous sinus thrombosis).

[g] Adverse Drug Reaction (ADR) identified post-marketing.

Table 5[d]. Adverse Drug Reactions by SOC and CIOMS Frequency (RA Program - A3921133)				
System Organ Class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**
Infections and infestations	Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Nasopharyngitis Pharyngitis Tuberculosis	Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection Sepsis Arthritis bacterial[a]	Urosepsis Disseminated tuberculosis *Pneumocystis jirovecii* pneumonia Pneumonia bacterial	Bacteremia Pneumonia pneumococcal Cytomegalovirus infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Non-melanoma skin cancers[b]		
Blood and lymphatic system disorders	Anemia Lymphopenia	Leukopenia Neutropenia		
Immune system disorders		Drug hypersensitivity		
Metabolism and nutrition disorders		Hyperlipidemia Dyslipidemia	Dehydration	
Psychiatric disorders		Insomnia		
Nervous system disorders	Headache	Paresthesia		

Table 5[d]. Adverse Drug Reactions by SOC and CIOMS Frequency (RA Program - A3921133)				
System Organ Class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very Rare <1/10,000**
Vascular disorders	Hypertension	Venous thromboembolism[c]		
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnea Sinus congestion		
Gastrointestinal disorders	Diarrhea Nausea	Abdominal pain Vomiting Gastritis Dyspepsia		
Hepatobiliary disorders		Hepatic steatosis		
Skin and subcutaneous tissue disorders		Rash Acne[e] Erythema Pruritus		
Musculoskeletal and connective tissue disorders	Arthralgia	Joint swelling Tendonitis	Musculoskeletal pain	
General disorders and administration site conditions	Edema peripheral	Pyrexia Fatigue		
Investigations		Blood cholesterol increased Weight increased Hepatic enzyme increased Transaminases increased	Gamma-glutamyltransferase increased Blood creatine phosphokinase increased Liver function test abnormal Blood creatinine increased Low density lipoprotein increased	
Injury, poisoning and procedural complications		Ligament sprain Muscle strain		

Abbreviations: ADR = adverse drug reaction; CIOMS = Council for International Organizations of Medical Sciences; NMSC = non-melanoma skin cancers; PT = preferred term; RA = rheumatoid arthritis; SOC = System Organ Class.

[a] The frequency of arthritis bacterial is determined by combined frequencies for PTs of arthritis bacterial and arthritis infective.

[b] NMSC identified as ADR in 2013; NMSC is not a PT: the frequency is determined by combining frequencies for PTs of basal cell cancer and squamous cell cancer of the skin.

[c] Venous thromboembolism (e.g., pulmonary embolism, deep vein thrombosis, and retinal venous thrombosis, cerebral venous sinus thrombosis).

[d] Table is based on incidence rates per 100 patient-years.

[e] Adverse Drug Reaction (ADR) identified post-marketing.

Overall Infections

Rheumatoid Arthritis

In the 6-month and 24-month, controlled Phase 3 clinical studies, the rates of infections in the 5 mg twice daily (total 616 patients) and 10 mg twice daily (total 642 patients) Tofacitinib (Xeljanz®) monotherapy group were 16.2% (100 patients), and 17.9% (115 patients), respectively, compared to 18.9% (23 patients) in the placebo group (total 122 patients). In studies of 6-month, 12-month, or 24-month duration with background DMARDs, the rates of infections in the 5 mg twice daily (total 973 patients) and 10 mg twice daily (total 969 patients) Tofacitinib (Xeljanz®) plus DMARD group were 21.3% (207 patients) and 21.8% (211 patients), respectively, compared to 18.4% (103 patients) in the placebo plus DMARD group (total 559 patients).

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 (Xeljanz®) in the long-term safety all exposure population (total 4,867 patients) was 46.1 patients with events per 100 patient-years (43.8 and 47.2 patients with 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 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively.

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

Serious Infections

Rheumatoid Arthritis

In the 6-month and 24-month, controlled clinical studies, the rate of serious infections in the 5 mg twice daily Tofacitinib (Xeljanz®) monotherapy group was 1.7 patients with events per 100 patient-years. In the 10 mg twice daily Tofacitinib (Xeljanz®) monotherapy group, the rate was 1.6 patients with events per 100 patient-years, the rate was 0 events per 100 patient-years for the placebo group and the rate was 1.9 patients with events per 100 patient-years for the methotrexate group.

In studies of 6-, 12- or 24-months duration, the rates of serious infections in the 5 mg twice daily and 10 mg twice daily Tofacitinib (Xeljanz®) plus DMARD groups were 3.6 and 3.4 patients with events per 100 patient-years, respectively, compared to 1.7 patients with events per 100 patient-years in the placebo plus DMARD group.

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 for 5 mg and 10 mg twice daily Tofacitinib (Xeljanz®) groups, respectively. The most common serious infections reported with

Tofacitinib (Xeljanz®) included pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis, and diverticulitis. Cases of opportunistic infections have been reported (see **section 4.4 Special Warnings and Precautions for Use**).

Of the 4271 patients who enrolled in Studies I to VI, a total of 608 rheumatoid arthritis patients were 65 years of age and older, including 85 patients 75 years and older. The frequency of serious infection among Tofacitinib (Xeljanz®)-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.

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

Viral Reactivation

In Tofacitinib (Xeljanz®) clinical trials, Japanese and Korean patients appear to have a higher rate of herpes zoster than that observed in other populations. Events of herpes zoster were reported in a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see **section 5.1 Pharmacodynamic Properties**).

Venous Thromboembolism

Rheumatoid Arthritis

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

Completed Rheumatoid Arthritis Studies

In the 4 to 12 week placebo period of randomized 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 PYs 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 PYs respectively.

In the full randomized 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 PYs 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 PYs respectively.

In the long term safety population that includes exposure during completed randomized 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 PYs 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 PYs respectively.

Clinical Experience in Methotrexate-Naïve Rheumatoid Arthritis Patients

Study VI was an active-controlled clinical trial in methotrexate-naïve RA patients (see **section 5.1 Pharmacodynamic Properties**). The safety experience in these patients was consistent with Studies I-V.

Laboratory Tests

Rheumatoid Arthritis

Lymphocytes

In the controlled clinical studies in rheumatoid arthritis, confirmed decreases in lymphocyte counts below 500 cells/mm^3 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 in rheumatoid arthritis, confirmed decreases in lymphocyte counts below 500 cells/mm^3 occurred in 1.3% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

Confirmed lymphocyte counts <500 cells/mm^3 were associated with an increased incidence of treated and serious infections (see **section 4.4 Special Warnings and Precautions for Use**).

Neutrophils

In the controlled clinical studies in rheumatoid arthritis, confirmed decreases in ANC below 1000 cells/mm^3 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 500 cells/mm^3 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 Special Warnings and Precautions for Use**).

Liver Enzyme Tests

Rheumatoid Arthritis

Confirmed increases in liver enzymes >3 times the upper limit of normal (3x 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 (Xeljanz®), or reduction in Tofacitinib (Xeljanz®) dose, resulted in decrease or normalization of liver enzymes.

In the controlled portion of the Phase 3 monotherapy study (0-3 months), (Study I, see **section 5.1 Pharmacodynamic Properties**), ALT elevations >3x ULN were observed in 1.65%, 0.41%, and 0% of patients receiving placebo, Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg, and 10 mg twice daily, respectively.

In the Phase 3 monotherapy study (0-24 months) (Study VI, see **section 5.1 Pharmacodynamic Properties**), ALT elevations >3x ULN were observed in 7.1%, 3.0%, and 3.0% of patients receiving methotrexate, Tofacitinib (Xeljanz®) 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 methotrexate, Tofacitinib (Xeljanz®) 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 Pharmacodynamic Properties**), ALT elevations >3x ULN were observed in 0.9%, 1.24% and 1.14% of patients receiving placebo, Tofacitinib (Xeljanz®) 5 mg, and 10 mg twice daily, respectively. In these studies, AST elevations >3x ULN were observed in 0.72%, 0.50% and 0.31% of patients receiving placebo, Tofacitinib (Xeljanz®) 5 mg, and 10 mg twice daily, respectively.

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

Lipids

Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were first assessed at one month following initiation of Tofacitinib (Xeljanz®) in the controlled double-blind clinical trials of rheumatoid arthritis. Increases were observed at this time point and remained stable thereafter.

Rheumatoid Arthritis

Changes in lipid parameters from baseline through the end of the study (6-24 months) in the controlled clinical studies in rheumatoid arthritis are summarized below:

- Mean LDL cholesterol increased by 15% in the Tofacitinib (Xeljanz®) 5 mg twice daily arm and 20% in the Tofacitinib (Xeljanz®) 10 mg twice daily arm at month 12, and increased by 16% in the Tofacitinib (Xeljanz®) 5 mg twice daily arm and 19% in the Tofacitinib (Xeljanz®) 10 mg twice daily arm at month 24.
- Mean HDL cholesterol increased by 17% in the Tofacitinib (Xeljanz®) 5 mg twice daily arm and 18% in the Tofacitinib (Xeljanz®) 10 mg twice daily arm at month 12, and increased by 19% in the Tofacitinib (Xeljanz®) 5 mg twice daily arm and 20% in the Tofacitinib (Xeljanz®) 10 mg twice daily arm at month 24.

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

Upon withdrawal of tofacitinib treatment, lipid levels returned to baseline.

In rheumatoid arthritis, Mean LDL cholesterol/HDL cholesterol ratios and Apolipoprotein B (ApoB)/ApoA1 ratios were essentially unchanged in Tofacitinib (Xeljanz®)-treated patients.

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.

4.9 Overdose and Treatment

There is no experience with overdose of Tofacitinib (Xeljanz®/Xeljanz® XR). There is no specific antidote for overdose with Tofacitinib (Xeljanz®/Xeljanz® XR). 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.

5.0 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

Tofacitinib is a potent, 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 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 interferons. At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling.

Pharmacodynamic Effect

In patients with rheumatoid arthritis, treatment up to 6 months with Tofacitinib (Xeljanz®) 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 (Xeljanz®) 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.

Following long-term treatment (median duration of Tofacitinib (Xeljanz®) 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+ natural killer cell counts showed a median increase of 73% from baseline. CD19+ B cell counts showed no further increases after long-term Tofacitinib (Xeljanz®) 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 (Xeljanz®) dosing in patients with rheumatoid arthritis were small, not dose-dependent and similar to those seen on placebo.

After treatment with Tofacitinib (Xeljanz®) in patients with rheumatoid arthritis, rapid decreases in serum C-reactive protein (CRP) were observed and maintained throughout dosing. Changes in CRP observed with Tofacitinib (Xeljanz®) 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 randomized 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 analyzed in their originally randomized 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for Tofacitinib (Xeljanz ®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) were 1.30 (0.29, 5.81), 3.45 (0.95, 12.54), and 2.34 (0.67, 8.16), respectively

In Tofacitinib (Xeljanz®) clinical studies that included 10 mg twice a day, incidence rates for all-cause mortality in patients treated with Tofacitinib (Xeljanz®) 10 mg twice a day have not been higher than rates in patients treated with Tofacitinib (Xeljanz®) 5 mg twice a day. Mortality rates in patients treated with Tofacitinib (Xeljanz®) are similar to those reported for patients with RA, PsO, PsA, AS, pcJIA and UC, treated with biologic therapies.

Infections

The IRs (95% CI) for all infections for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HR (95% CI) for herpes zoster with Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) were 3.17 (2.36, 4.27), 3.33 (2.48, 4.48), and 3.25 (2.46, 4.29), respectively.

Serious infections from non-interventional post approval safety study

Data from a non-interventional post approval safety study that evaluated tofacitinib in RA patients from a registry (US Corrona) showed that a numerically higher incidence rate of serious infection was observed for the 11 mg prolonged-release tablet administered once daily than the 5 mg film-coated tablet administered twice daily. Crude incidence rates (95% CI) (i.e., not adjusted for age or sex) from availability of each formulation at 12 months following initiation of treatment were 3.45 (1.93, 5.69) and 2.78 (1.74, 4.21) and at 36 months were 4.71 (3.08, 6.91) and 2.79 (2.01, 3.77) patients with events per 100 patient-years in the 11 mg prolonged-release tablet once daily and 5 mg film-coated tablet twice daily groups, respectively. The unadjusted hazard ratio was 1.30 (95% CI: 0.67, 2.50) at 12 months and 1.93 (95% CI: 1.15, 3.24) at 36 months for the 11 mg prolonged-release once daily dose compared to the 5 mg film-coated twice daily dose. Data is based on a small number of patients with events observed with relatively large confidence intervals and limited follow up time available in the 11 mg prolonged-release once daily dose group after 24 months.

Thromboembolism

Venous Thromboembolism

The IRs (95% CI) for VTE for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HR (95% CI) for VTE with Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HR (95% CI) for PE with Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) were 2.93 (0.79, 10.83), 8.26 (2.49, 27.43), and 5.53 (1.70, 18.02), respectively. In tofacitinib-treated patients where PE was observed, the majority (97%) had VTE risk factors.

The IRs (95% CI) for DVT for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HR (95% CI) for DVT with Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 randomized 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 ≥2× ULN at 12 months treatment versus those with D-dimer level <2× 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 ≥2× 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HR (95% CI) for ATE with Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) were 1.24 (0.81, 1.91), 1.43 (0.94, 2.18), and 1.33 (0.91, 1.94), respectively.

In the Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®), 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, all Tofacitinib (Xeljanz®) (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 PYs respectively. Compared with TNFi, the HRs (95% CI) for Tofacitinib (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 10 mg twice daily, and all Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily treatment arm were 52.83, 6.01, and 1.68, respectively. The percentages for the Tofacitinib (Xeljanz®) 10 mg twice daily treatment arm were 54.46, 6.54, and 1.97, respectively. The percentages for all Tofacitinib (Xeljanz®) (combines Tofacitinib (Xeljanz®) 5 mg twice daily and Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily treatment arm were 45.84, 3.21, and 0.98, respectively. The percentages for the Tofacitinib (Xeljanz®) 10 mg twice daily treatment arm were 51.58, 4.57, and 1.62, respectively. The percentages for all Tofacitinib (Xeljanz®) (combines Tofacitinib (Xeljanz®) 5 mg twice daily and Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 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 (Xeljanz®) 5 mg twice daily, Tofacitinib (Xeljanz®) 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

Rheumatoid Arthritis

Tofacitinib (Xeljanz® XR) 11 mg once daily has demonstrated pharmacokinetic equivalence (AUC and C_{max}) to Tofacitinib (Xeljanz®) 5 mg twice daily. The recommended dose of Tofacitinib (Xeljanz® XR) is 11 mg once daily. All information provided in this section is applicable to Tofacitinib (Xeljanz® XR).

The efficacy and safety of Tofacitinib (Xeljanz®) were assessed in six randomized, double-blind, controlled multicenter studies in patients >18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 tender and 6 swollen joints at randomization (4 swollen and tender joints for Study II). Tofacitinib (Xeljanz®), 5 or 10 mg twice daily, was given as monotherapy (Study I) and in combination with DMARDs (Study II) in patients with an inadequate response to those drugs, and in combination with MTX in patients with either an inadequate response to MTX (Studies III and Study IV) or inadequate efficacy or lack of tolerance to at least one approved TNF-inhibiting biologic agent (Study V).

Study I was a 6-month monotherapy study in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (non-biologic or biologic) received Tofacitinib (Xeljanz®) 5 or 10 mg twice daily or placebo. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of Tofacitinib (Xeljanz®) 5 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 was a 12-month study in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a non-biologic DMARD received Tofacitinib (Xeljanz®) 5 or 10 mg twice daily or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). At the Month 3 visit, non-responding patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of Tofacitinib (Xeljanz®) 5 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 was a 12-month study in which 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX. Patients received Tofacitinib (Xeljanz®) 5 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 was a 2-year study with a planned analysis at 1 year in which 797 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received Tofacitinib (Xeljanz®) 5 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 was a 6-month study in which 399 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to at least one approved TNF-inhibiting biologic agent received Tofacitinib (Xeljanz®) 5 or 10 mg twice daily or placebo added to background MTX. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of Tofacitinib (Xeljanz®) 5 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 was a 2-year monotherapy study with a planned analysis at 1 year in which 952 MTX-naïve patients with moderate to severe active rheumatoid arthritis received Tofacitinib (Xeljanz®) 5 or 10 mg twice daily or MTX dose-titrated over 8 weeks from 10 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

ACR Response

The percentages of Tofacitinib (Xeljanz®)-treated patients achieving ACR20, ACR50 and ACR70 responses in Studies I, II, IV, V and VI are shown in Table 6. In all studies, patients treated with either 5 or 10 mg twice daily Tofacitinib (Xeljanz®) had statistically significant ACR20, ACR50 and ACR70 response rates at Month 3 and Month 6 vs. placebo (or vs. MTX in Study VI) treated patients.

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

In Study VI (Table 6), 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 RA signs and symptoms 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.

During the 3 month (Studies I and V) and 6 month (Studies II, III, and IV) controlled portions of the studies, patients treated with Tofacitinib (Xeljanz®) at a dose of 10 mg twice daily generally had higher response rates compared to patients treated with Tofacitinib (Xeljanz®) 5 mg twice daily. In Study III, the primary endpoints were 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. The data for these primary outcomes were 51.5, 52.6, 47.2 and 28.3%; -0.55, -0.61, -0.49 and -0.24; and 6.2%, 12.5%, 6.7% and 1.1% for the 5 mg twice daily Tofacitinib (Xeljanz®), 10 mg twice daily Tofacitinib (Xeljanz®), 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 and 10 mg twice daily Tofacitinib (Xeljanz®) groups were significantly greater than adalimumab 19.9%, 21.9% 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 in patients treated with 5 mg or 10 mg twice daily Tofacitinib (Xeljanz®), 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 in all studies.

DAS28-4(ESR) Response

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 and 1.9–2.2 were observed in 5 mg and 10 mg Tofacitinib (Xeljanz®)-treated patients, respectively, 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 or 10 mg tofacitinib (6%–9% and 13%–16%, respectively) compared to 1%–3% of placebo patients at 6 months. In Study III, the percentages of patients achieving DAS28-4(ESR) <2.6 observed for Tofacitinib (Xeljanz®) 5 mg twice daily, 10 mg twice daily, and adalimumab at Month 6 were 6.2%, 12.5%, and 6.7%, respectively.

In a pooled analysis of the Phase 3 studies, the 10 mg twice daily dose provided increased benefit over the 5 mg twice daily dose in multiple measures of signs and symptoms: improvement from baseline (ACR20, ACR50, and ACR70 response rates), and achievement of targeted disease activity state (either DAS28-4(ESR) <2.6 or ≤3.2). Greater benefits of 10 mg versus 5 mg were shown in the more stringent measures (i.e., ACR70 and DAS28-4 (ESR) <2.6 response rates).

Table 6: Proportion of Patients with an ACR Response

Study I: DMARD Inadequate Responders				
Response Rate (%)	**Time**	**Placebo N = 120**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily Monotherapy N = 241**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily Monotherapy N = 242**
ACR20	Month 3	27	60	66
	Month 6	NA	69	71
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
ACR50	Month 3	13	31	37
	Month 6	NA	42	47
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
ACR70	Month 3	6	15	20
	Month 6	NA	22	29
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
Study II: DMARD Inadequate Responders DMARD(s), Most Commonly MTX				
Response Rate (%)	**Time**	**Placebo N = 157**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily DMARD(s) N = 311**	**Tofacitinib (Xeljanz®) 10 mg DMARD(s) N = 309**
ACR20	Month 3	27	56	65
	Month 6	31	53	58
	Month 12	NA	51	57
ACR50	Month 3	10	27	34
	Month 6	13	34	37
	Month 12	NA	33	43
ACR70	Month 3	2	8	14
	Month 6	3	13	16
	Month 12	NA	19	26
Study IV: MTX Inadequate Responders				

Response Rate (%)	Time	Placebo + MTX N = 154	Tofacitinib (Xeljanz®) 5 mg Twice Daily + MTX N = 309	Tofacitinib (Xeljanz®) 10 mg Twice Daily + MTX N = 309
ACR20	Month 3	27	56	66
	Month 6	25	51	62
	Month 12	NA	49	56
	Month 24	NA	41	50
ACR50	Month 3	8	29	36
	Month 6	8	32	44
	Month 12	NA	32	39
	Month 24	NA	29	40
ACR70	Month 3	3	11	17
	Month 6	1	15	22
	Month 12	NA	19	27
	Month 24	NA	17	26
Study V: TNF Inhibitor Inadequate Responders				
Response Rate (%)	**Time**	**Placebo + MTX** **N = 131**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily + MTX** **N = 132**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily + MTX** **N = 133**
ACR20	Month 3	24	42	48
	Month 6	NA	52	55
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
ACR50	Month 3	8	27	28
	Month 6	NA	37	30
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
ACR70	Month 3	2	14	11
	Month 6	NA	16	16
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
Study VI: MTX-naïve				
Response Rate (%)	**Time**	**MTX** **N = 184**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily Monotherapy N = 369**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily Monotherapy N = 394**
ACR20	Month 3	52	70	78
	Month 6	51	71	76
	Month 12	51	68	72
	Month 24	42	64	64
ACR50	Month 3	20	40	50
	Month 6	27	47	56
	Month 12	34	50	56
	Month 24	28	49	49
ACR70	Month 3	5	20	27
	Month 6	12	25	38
	Month 12	15	29	38
	Month 24	15	34	38

The results of the proportion of patients with an ACR Response for Studies I, II, IV, V and VI are shown in Table 6. Similar results were observed in Study III.

The results of the components of the ACR response criteria for Studies IV and V are shown in Table 7. Similar results were observed in Studies I, II and III.

Table 7: Components of ACR Response at Month 3 in Studies IV and V

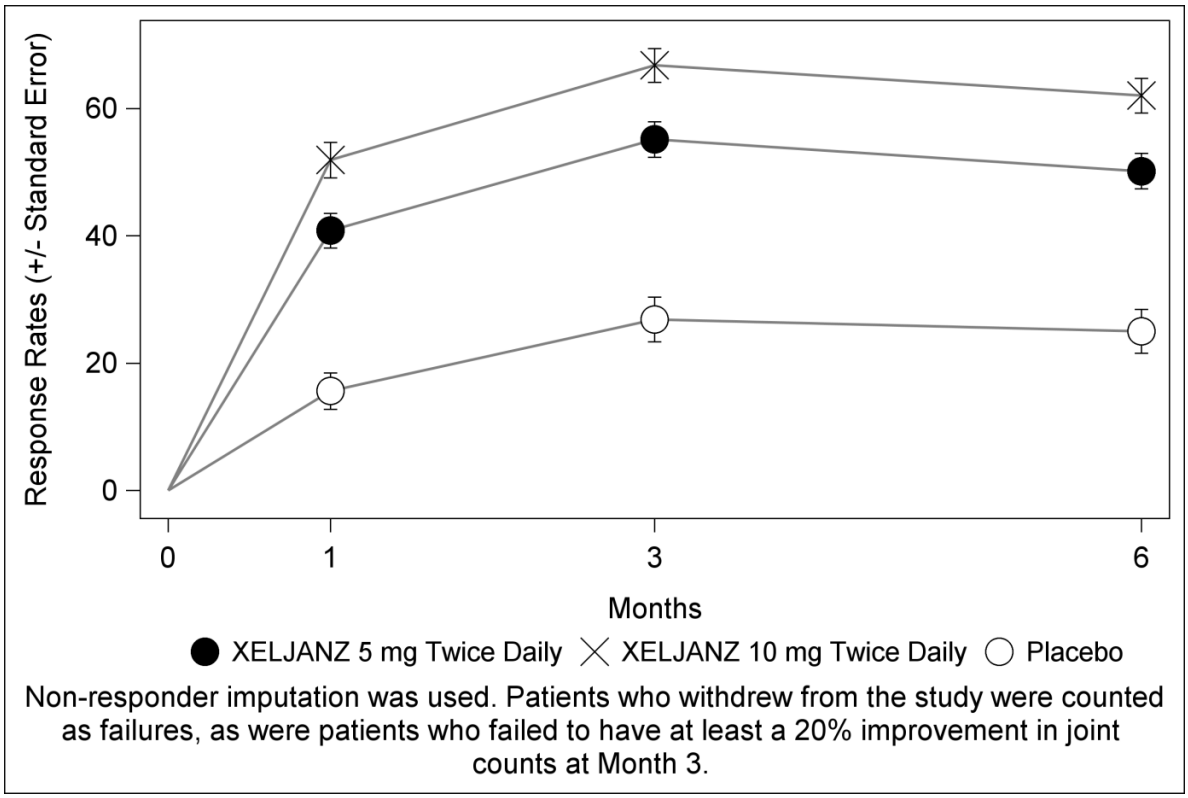
Study IV: MTX Inadequate Responders				
Component	**Time**	**Placebo + MTX N = 156**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily + MTX N = 316**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily + MTX N = 309**
Number of tender joints (0-68)	Baseline	23	24	23
	Month 3	18	13	10
Number of swollen joints (0-66)	Baseline	14	14	14
	Month 3	10	6	6
Pain[a]	Baseline	55	58	58
	Month 3	47	35	29
Patient global assessment[a]	Baseline	54	58	57
	Month 3	47	35	29
Disability index (HAQ-DI)[b]	Baseline	1.31	1.41	1.39
	Month 3	1.19	1.00	0.84
Physician global assessment[a]	Baseline	56	59	58
	Month 3	43	30	25
CRP (mg/L)	Baseline	13.7	15.5	17.0
	Month 3	14.6	6.9	4.4
Study V: TNF Inhibitor Inadequate Responders				
Component	**Time**	**Placebo + MTX N = 132**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily + MTX N = 133**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily + MTX N = 134**
Number of tender joints (0-68)	Baseline	28	28	28
	Month 3	21	16	13
Number of swollen joints (0-66)	Baseline	17	16	17
	Month 3	12	8	7
Pain[a]	Baseline	61	66	60
	Month 3	53	39	38
Patient global assessment[a]	Baseline	62	65	59
	Month 3	53	41	37
Disability index (HAQ-DI)[b]	Baseline	1.63	1.60	1.50
	Month 3	1.44	1.20	1.10
Physician global assessment[a]	Baseline	64	65	59
	Month 3	44	35	31
CRP (mg/L)	Baseline	16.7	19.3	15.7
	Month 3	18.2	6.2	4.8

[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

The percent of ACR20 responders by visit for Study IV is shown in Figure 1. Similar responses were observed in Studies I, II, III and V.

Figure 1: Percentage of ACR20 Responders by Visit for Study IV



Radiographic Response

Two studies were conducted to evaluate the effect of Tofacitinib (Xeljanz®) on structural joint damage. In Study IV and Study VI, inhibition of progression of structural joint damage was assessed radiographically and expressed as mean change from baseline in mTSS and its components, the erosion score and joint space narrowing (JSN) score, at Months 6 and 12. The proportion of patients with no radiographic progression (mTSS change less than or equal to 0.5) was also assessed.

In Study IV, Tofacitinib (Xeljanz®) 10 mg twice daily plus background MTX resulted in significantly greater inhibition of the progression of structural damage compared to placebo plus MTX at Months 6 and 12. When given at a dose of 5 mg twice daily, Tofacitinib (Xeljanz®) plus MTX exhibited similar effects on mean progression of structural damage (not statistically significant). Analysis on erosion and JSN score were consistent with overall results. These results are shown in Table 8.

In the placebo plus MTX group, 78% of patients experienced no radiographic progression at Month 6 compared to 89% and 87% of patients treated with Tofacitinib (Xeljanz®) 5 or 10 mg twice daily respectively, plus MTX, both significant vs. placebo plus MTX.

Table 8: Radiographic Changes at Months 6 and 12

	Study IV				
	Placebo + MTX **N = 139** **Mean (SD)[a]**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily + MTX** **N = 277** **Mean (SD)[a]**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily + MTX** **Mean Difference from Placebo[b] (CI)**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily + MTX** **N = 290** **Mean (SD)[a]**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily + MTX** **Mean Difference from Placebo[b] (CI)**
mTSS[c]					
Baseline	33 (42)	31 (48)	-	37 (54)	-
Month 6	0.5 (2.0)	0.1 (1.7)	-0.3 (-0.7, 0.0)	0.1 (2.0)	-0.4 (-0.8, 0.0)
Month 12	1.0 (3.9)	0.3 (3.0)	-0.6 (-1.3, 0.0)	0.1 (2.9)	-0.9 (-1.5, -0.2)
Erosion score[c]					
Baseline	14 (19)	14 (24)	-	18 (28)	-
Month 6	0.1 (1.0)	0.1 (1.0)	-0.1 (-0.3, 0.1)	0.0 (0.7)	-0.1 (-0.3, 0.1)
Month 12	0.3 (2.0)	0.2 (1.7)	-0.1 (-0.4, 0.2)	0.0 (1.1)	-0.3 (-0.6, 0.0)
JSN score[c]					
Baseline	18 (24)	17 (25)	-	20 (28)	-
Month 6	0.3 (1.5)	0.1 (1.1)	-0.3 (-0.6, 0.1)	0.1 (1.8)	-0.3 (-0.6, 0.0)
Month 12	0.7 (2.9)	0.1 (1.9)	-0.5 (-1.0, 0.0)	0.1 (2.6)	-0.6 (-1.1, -0.1)

[a] SD = Standard Deviation.
[b] Difference between least squares means tofacitinib (Xeljanz®) minus placebo (95% CI = 95% confidence interval).
[c] Month 6 and Month 12 data are mean change from baseline.

In Study VI, Tofacitinib (Xeljanz®) monotherapy resulted in significantly greater inhibition of the progression of structural damage compared to MTX at Months 6 and 12 as shown in Table 9, which was also maintained at Month 24. Analyses of erosion and JSN scores were consistent with overall results.

In the MTX group, 70% of patients experienced no radiographic progression at Month 6 compared to 84% and 90% of patients treated with tofacitinib 5 or 10 mg twice daily respectively, both significant vs. MTX.

Table 9: Radiographic Changes at Months 6 and 12

	Study VI				
	MTX **N = 166** **Mean (SD)[a]**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily** **N = 346** **Mean (SD)[a]**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily Mean Difference from MTX[b] (CI)**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily** **N = 369** **Mean (SD)[a]**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily Mean Difference from MTX[b] (CI)**
mTSS[c] Baseline Month 6 Month 12	17 (29) 0.8 (2.7) 1.3 (3.7)	20 (40) 0.2 (2.3) 0.4 (3.0)	- -0.7 (-1.0, -0.3) -0.9 (-1.4, -0.4)	19 (39) 0.0 (1.2) 0.0 (1.5)	- -0.8 (-1.2, -0.4) -1.3 (-1.8, -0.8)
Erosion score[c] Baseline Month 6 Month 12	8 (15) 0.5 (1.9) 0.6 (2.2)	10 (21) 0.1 (1.4) 0.1 (1.6)	- -0.4 (-0.7, -0.2) -0.6 (-0.8, -0.3)	9 (20) 0.0 (0.7) 0.0 (1.0)	- -0.5 (-0.7, -0.3) -0.7 (-0.9, -0.4)
JSN score[c] Baseline Month 6 Month 12	8 (16) 0.4 (1.3) 0.6 (2.1)	11 (21) 0.1 (1.4) 0.3 (2.1)	- -0.2 (-0.5, 0.0) -0.4 (-0.7, 0.0)	9 (20) 0.1 (0.9) 0.0 (0.9)	- -0.3 (-0.5, -0.1) -0.6 (-0.9, -0.3)

[a] SD = Standard Deviation
[b] Difference between least squares means Tofacitinib (Xeljanz®) minus MTX (95% CI = 95% confidence interval)
[c] Month 6 and Month 12 data are mean change from baseline

Physical Function Response and Health Related Outcomes

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving Tofacitinib (Xeljanz®) 5 or 10 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 (Xeljanz®) 5 or 10 mg twice daily-treated patients exhibited significantly greater improved physical functioning compared to placebo as early as Week 2 in Studies I and II. In Study III, mean HAQ-DI improvements were maintained to 12 months in Tofacitinib (Xeljanz®)-treated patients. Mean HAQ-DI improvements were maintained for 36 months in the ongoing open-label extension studies. Compared with adalimumab-treated patients, at Month 3, patients in the Tofacitinib (Xeljanz®) 5 mg twice daily had similar decreases from baseline in HAQ-DI values and patients in 10 mg twice daily group had significantly greater decreases in HAQ-DI. The mean change in HAQ-DI from baseline to Month 3 in Studies I to VI are shown in Table 10.

Table 10: Mean Change from Baseline in HAQ-DI

Study I: DMARD Inadequate Responders			
Time	**Placebo** **N = 109**	**Tofacitinib (Xeljanz®) 5 mg Monotherapy Twice Daily** **N = 237**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily Monotherapy** **N = 227**
LS Mean Change in HAQ-DI at Month 3[a]	-0.19	-0.50**	-0.57**
Study II: DMARD Inadequate Responders			
	Placebo + DMARD(s) **N=147**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily + DMARD(s)** **N = 292**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily + DMARD(s)** **N = 292**
LS Mean Change in HAQ-DI at Month 3[a]	-0.21	-0.46**	-0.56**

Study III: MTX Inadequate Responders				
	Placebo + MTX **N=98**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily + MTX** **N = 188**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily + MTX** **N = 185**	**Adalimumab 40 mg QOW + MTX** **N = 190**
LS Mean Change in HAQ-DI at Month 3[a]	-0.24	-0.55**	-0.61**	-0.49**

Study IV: MTX Inadequate Responders			
	Placebo + MTX **N = 146**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily + MTX** **N = 294**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily + MTX** **N = 300**
LS Mean Change in HAQ-DI at Month 3[a]	-0.15	-0.40[b]	-0.54

Study V: TNF Inhibitor Inadequate Responders			
	Placebo **N = 118**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily + MTX** **N = 117**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily + MTX** **N = 125**
LS Mean Change in HAQ-DI at Month 3[a]	-0.18	-0.43**	-0.46**

Study VI: MTX-naïve: Monotherapy			
	Placebo + MTX **N = 171**	**Tofacitinib (Xeljanz®) 5 mg Twice Daily Monotherapy** **N = 355**	**Tofacitinib (Xeljanz®) 10 mg Twice Daily Monotherapy** **N = 381**
LS Mean Change in HAQ-DI at Month 3[a]	-0.47	-0.75**	-0.85**

[a.] Primary efficacy time point.
[b.] Statistical significance could not be declared in Study IV due to step-down procedure.
** $p<0.0001$, Tofacitinib (Xeljanz®) 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.
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

Health-related quality of life was assessed by the Short Form Health Survey (SF-36) in all 5 studies. In these studies, patients receiving Tofacitinib (Xeljanz®) 10 mg twice daily demonstrated 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. Both Tofacitinib (Xeljanz®)-treated groups exhibited significantly greater improvement from baseline compared to placebo in all 8 domains as well as PCS and 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 (Xeljanz®)-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 (Xeljanz®) 5 or 10 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 (Xeljanz®)-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 (Xeljanz®) 5 or 10 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 (Xeljanz®)-treated patients.

Improvement in productivity was evaluated using the Work Limitations Questionnaire (WLQ) scale at Month 3 in all studies. Patients receiving Tofacitinib (Xeljanz®) 10 mg twice daily demonstrated significantly greater improvement from baseline in the Overall Output Summary Scale compared to placebo in Studies III, IV, and V. In Studies III and IV, mean Overall Output improvements were maintained to 12 months in Tofacitinib (Xeljanz®) 10 mg twice daily-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. Efficacy was maintained in all tofacitinib treatment groups 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 randomized PASS in RA patients 50 years and older with at least one additional CV risk factor, as well as in completed open-label, long-term follow-up studies up to 8 years.

5.2 Pharmacokinetic Properties

Tofacitinib (Xeljanz®)

The PK profile of Tofacitinib (Xeljanz®) is characterized 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.

Tofacitinib (Xeljanz® XR)

Following oral administration of Tofacitinib (Xeljanz® XR), peak plasma concentrations are reached at 4 hours and half-life is about 6 to 8 hours. Steady state concentrations are achieved within 48 hours with negligible accumulation after once daily administration. AUC and C_{max} of tofacitinib for Xeljanz® XR 11 mg administered once daily are bioequivalent to those of Tofacitinib (Xeljanz®) 5 mg administered twice daily.

Absorption and Distribution

Tofacitinib is well-absorbed, with an oral bioavailability of 74% following administration of Tofacitinib (Xeljanz®). Co-administration of Tofacitinib (Xeljanz®) 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.

After intravenous administration, the volume of distribution is 87 L. Approximately 40% of circulating tofacitinib is bound to 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.

Tofacitinib (Xeljanz® XR)

Co-administration of Tofacitinib (Xeljanz® XR) with a high-fat meal resulted in no changes in AUC while C_{max} was increased by 27% and T_{max} was extended by approximately 1 hour.

Metabolism and Elimination

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. All metabolites have been observed in animal species and are predicted to have ≤10% of the potency of tofacitinib for JAK1/3 inhibition. No evidence of stereo conversion in human samples was detected. 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, OAT P1B1/1B3, OCT2, organic anion transporter (OAT) 1/3, or multidrug resistance-associated protein (MRP) at clinically meaningful concentrations.

Pharmacokinetic data and dosing recommendations for special populations and drug interactions are provided in Figure 2.

Modifications required for special populations are described in **section 4.2 Dosage and Method of Administration**.

Pharmacokinetics in RA Patients

Population PK analysis in rheumatoid arthritis 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 White, Black and Asian patients. 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 (Xeljanz®) is estimated to be approximately 27%.

Renal Impairment

Patients with mild, moderate, and severe renal impairment had 37%, 43% and 123% higher AUC, respectively, compared with healthy patients (see **section 4.2 Dosage and Method of Administration**). In patients with end-stage renal disease, the contribution of dialysis to the total clearance of tofacitinib was relatively small.

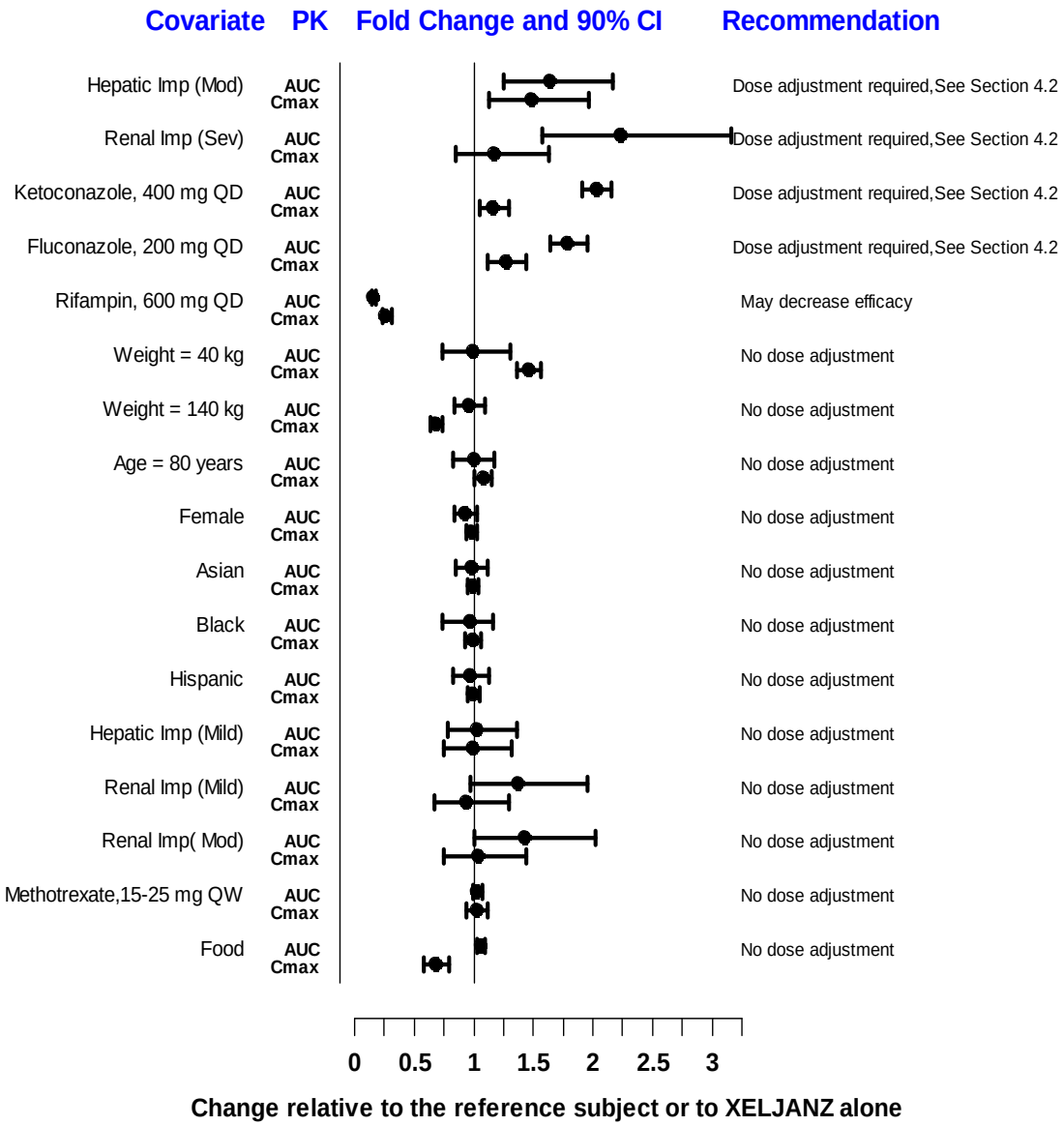
Hepatic Impairment

Patients with mild and moderate hepatic impairment had 3% and 65% higher AUC, respectively, compared with healthy patients. Patients with severe hepatic impairment were not studied (see **section 4.2 Dosage and Method of Administration**).

Pediatric Population

The pharmacokinetics, safety and efficacy of Tofacitinib in pediatric patients have not been established for rheumatoid arthritis.

Figure 2: Tofacitinib (Xeljanz®/Xeljanz® XR) Dosing Recommendation Based on Pharmacokinetic Data*



Weight, age, gender and race comparisons are based on RA patient data, with reference values of 70 kg, 55 years, male and White, respectively.

Note: Reference groups for renal and hepatic impairment data are subjects with normal renal or hepatic function, respectively; reference group for drug interaction and food effect studies is administration of Tofacitinib (Xeljanz®) alone: Mod = moderate; Sev = severe; Imp = impairment.

*Dose adjustment required for special populations are described in **section 4.2 Dosage and Method of Administration**.

5.3 Preclinical Safety Data

In non-clinical studies, effects were observed on the immune and hematopoietic systems that were attributed to the pharmacological properties (JAK inhibition) of tofacitinib. Secondary effects from immunosuppression, such as bacterial and viral infections and lymphoma were observed at clinically relevant doses. Other findings at doses well above human exposures included effects on the liver, lung and gastrointestinal systems.

Lymphoma was observed in 3 of 8 adult and 0 of 14 juvenile monkeys dosed with tofacitinib at 5 mg/kg twice daily. The no observed adverse effect level (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 approximately half of the unbound AUC at 10 mg twice daily and similar to the unbound AUC at 5 mg twice daily in humans.

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

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 ~19-fold the human AUC at 10 mg twice daily). Benign Leydig cell tumors were observed in rats: benign Leydig cell tumors in rats are not associated with a risk of Leydig cell tumors in humans. Hibernomas (malignancy of brown adipose tissue) were observed in female rats at doses ≥30 mg/kg/day (unbound drug AUC of ~41-fold the human AUC at 10 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 ~94-fold the human AUC at 10 mg twice daily).

Tofacitinib was shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility, parturition, and peri-/post-natal development. Tofacitinib had no effects on male fertility, sperm motility, or sperm concentration. Tofacitinib was secreted in milk of lactating rats. In studies conducted in juvenile rats and monkeys tofacitinib-related effects on the immune system were similar to those in adult animals. There were no tofacitinib-related effects on reproductive system or bone development in males or females.

6.0 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tofacitinib (Xeljanz®) 5 mg film-coated tablet:
Tablet core:
microcrystalline cellulose
lactose monohydrate
croscarmellose sodium
magnesium stearate

Film coat:
HPMC 2910/hypromellose
titanium dioxide
lactose monohydrate
macrogol/PEG 3350
triacetin
purified water

Tofacitinib (Xeljanz® XR) 11 mg extended release tablet:
Tablet core:
sorbitol
hydroxyethyl cellulose

copovidone
magnesium stearate

Film coat:
acetone
methanol
cellulose acetate
hydroxypropyl cellulose
HPMC 2910/hypromellose
titanium dioxide
triacetin
red iron oxide
purified water
Printing ink containing shellac glaze (20% esterified) in ethanol, isopropyl alcohol, ammonium hydroxide, N-butyl alcohol, propylene glycol, black iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

Please see outer package for the expiry date.

6.4 Storage Condition(s)

Store at temperatures not exceeding 30°C.

6.5 Availability

5 mg film-coated tablet: Alu/Alu-PVC Blister Pack of 14's (Box of 56's).

11 mg extended release tablet: Square HDPE bottle with polypropylene child-resistant closure and desiccant x 30's.

6.6 Special Precautions for Disposal and Other Handling

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7.0 FDA REGISTRATION NUMBER

5 mg film-coated tablet:	DR-XY46172
11 mg extended release tablet:	DR-XY46398

8.0 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

5 mg film-coated tablet:	04 Dec 2017
11 mg extended release tablet:	16 Jul 2018

Keep out of reach of children.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of any adverse drug reaction.

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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For Tofacitinib (Xeljanz® XR):

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