XELJANZ™

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ.
- If a serious infection develops, interrupt XELJANZ until the infection is controlled.
- Prior to starting XELJANZ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ.
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative.
- Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

1. Name of the Medicinal Product

1.1 Product name

XELJANZ™

1.2 Strength

5 mg

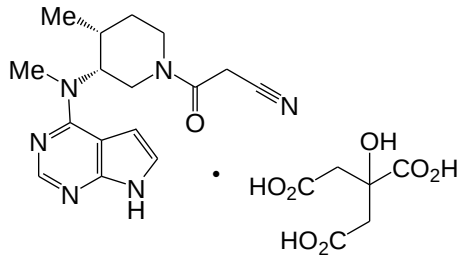
1.3 Pharmaceutical dosage form

Film-coated tablets

2. Qualitative and Quantitative Composition

2.1 Qualitative declaration

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 $C_{16}H_{20}N_6O \cdot C_6H_8O_7$ and its chemical structure is provided below:



2.2 Quantitative declaration

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

Excipients with known effect:
Each 5 mg tablet also contains 62.567 mg lactose monohydrate.
For a full list of excipients, see Section 6.1.

3. Pharmaceutical Form

Film-coated tablets

The 5 mg tablets are white round, film-coated tablets with “Pfizer” on one side and “JKI5” on the other side.

4. Clinical Particulars

4.1 Therapeutic indication

XELJANZ (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.

4.2 Posology and method of administration

Posology

XELJANZ may be used as monotherapy or in combination with methotrexate (MTX) or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs). The recommended dose is 5 mg administered twice daily.

XELJANZ has not been studied and its use should be avoided in combination with biological DMARDs, such as tumor necrosis factor (TNF) antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies and 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.

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

Dose Adjustments due to Laboratory Abnormalities (see Section 4.4)

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 XELJANZ 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 Warnings and Precautions [Section 4.4])	
Lab Value (cells/mm^3)	**Recommendation**
Lymphocyte count $\geq$ 500	Maintain dose
Lymphocyte count < 500 (Confirmed by repeat testing)	Discontinue XELJANZ

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

Table 2: Dose Adjustments for Neutropenia

Low ANC (see Warnings and Precautions [Section 4.4])	
Lab Value (cells/mm^3)	**Recommendation**
ANC > 1000	Maintain dose.

Low ANC (see Warnings and Precautions [Section 4.4])	
Lab Value (cells/mm^3)	**Recommendation**
ANC 500-1000	For persistent decreases in this range, reduce XELJANZ dose or interrupt dosing until ANC is > 1000. When ANC is > 1000, resume XELJANZ 5 mg twice daily.
ANC < 500 (Confirmed by repeat testing)	Discontinue XELJANZ.

It is recommended that XELJANZ not be initiated in patients with hemoglobin < 9 g/dL.

Table 3: Dose Adjustments for Anemia

Low Hemoglobin Value (see Warnings and Precautions [Section 4.4])	
Lab Value (g/dL)	**Recommendation**
≤ 2 g/dL decrease and ≥ 9.0 g/dL	Maintain dose.
> 2 g/dL decrease or < 8.0 g/dL (Confirmed by repeat testing)	Interrupt the administration of XELJANZ until hemoglobin values have normalized.

Special Populations

Renal Impairment

No dose adjustment is required in patients with mild renal impairment. XELJANZ dosage should be reduced to 5 mg once daily in patients with moderate or severe renal impairment (including but not limited to those undergoing hemodialysis) (see Sections 4.4 and 5.2).

Hepatic Impairment

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

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

XELJANZ dosage should be reduced to 5 mg once daily in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole). XELJANZ dosage should be reduced to 5 mg once daily in patients

receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

Patients Receiving Inducers of Cytochrome P450 (CYP3A4)

Co-administration of XELJANZ with potent CYP inducers (e.g., rifampin) may result in loss of or reduced clinical response (see Section 4.5).

Elderly Patients (≥ 65 years)

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

Pediatric

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

Method of Administration

XELJANZ is given orally with or without food.

4.3 Contraindications

Do not use XELJANZ if patients

- Have hypersensitivity to tofacitinib or to any of the excipients
- Have serious infection
- Have serious hepatic disease

4.4 Warnings and Precautions

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 XELJANZ. The most common serious infections reported with 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 XELJANZ. Some patients have presented with disseminated rather than localized disease, and 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). Some of these serious infections resulted in death. Opportunistic infections were also reported in the study.

XELJANZ 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 XELJANZ 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 XELJANZ. XELJANZ 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 XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes (see Section 4.8). Caution is also recommended in patients with a history of chronic lung disease as they may be more prone to infections. Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with XELJANZ, 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.

Tuberculosis

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

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

Antituberculosis therapy should also be considered prior to administration of XELJANZ 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 XELJANZ. 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). Post-marketing cases of hepatitis B reactivation have been reported in patients treated with XELJANZ. The impact of XELJANZ 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 XELJANZ.

Venous Thromboembolism

Venous thromboembolism (VTE) has been observed in patients taking XELJANZ in clinical trials and post-marketing reporting. 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 compared to TNF inhibitor (see Section 5.1). Many of these PE events were serious and some resulted in death. PE events were reported more frequently in this study in patients taking tofacitinib relative to other studies across the tofacitinib program (see Sections 4.8 and 5.1).

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

Assess patients for VTE risk factors before starting treatment and periodically during treatment. Use XELJANZ 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). 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).

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

Consider the risks and benefits of XELJANZ 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 XELJANZ in patients who develop a malignancy. The possibility exists for XELJANZ 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). 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).

Lymphomas have been observed in patients treated with XELJANZ and in patients treated with 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). 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 XELJANZ in the development of lymphoma is uncertain.

Lung cancers have been observed in patients treated with XELJANZ. Lung cancers were also observed in patients treated with 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 XELJANZ 10 mg twice daily compared with TNF inhibitor (see Section 5.1). Of the 30 lung cancers reported in the study in patients taking tofacitinib, all but 2 were in patients who were current or past smokers. Patients with rheumatoid arthritis may be at higher risk than the general population for the development of lung cancer. The role of XELJANZ 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 XELJANZ on the development and course of malignancies is not known.

Recommendations for non-melanoma skin cancer are presented below.

In controlled Phase 3 clinical studies in rheumatoid arthritis patients, 26 malignancies (excluding NMSC) including 5 lymphoma were diagnosed in 26 patients receiving XELJANZ/XELJANZ 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 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 XELJANZ groups.

In the long-term safety population (4867 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 XELJANZ compared with TNF inhibitor (see Section 5.1). 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. 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). 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.

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). The role of JAK inhibition in these events is not known. 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 XELJANZ therapy. Events were primarily reported as diverticular perforation, peritonitis, abdominal abscess and appendicitis. All 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. XELJANZ to the development of gastrointestinal perforations is not known.

XELJANZ 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 XELJANZ 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 XELJANZ 5 mg twice daily, 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 XELJANZ and TNF inhibitor treatment groups (see Section 5.1).

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 XELJANZ. 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 XELJANZ 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 XELJANZ is not recommended. Lymphocytes should be monitored at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts, see Section 4.2.

Neutrophils

Treatment with XELJANZ was associated with an increased incidence of neutropenia (< 2000 cells/mm^3) compared to placebo. It is not recommended to initiate XELJANZ treatment in patients with a low neutrophil count (i.e., ANC < 1000 cells/mm^3). For patients who develop a persistent ANC of 500-1000 cells/mm^3, reduce XELJANZ dose or interrupt dosing until ANC is > 1000 cells/mm^3. In patients who develop a confirmed absolute neutrophil count < 500 cells/mm^3 treatment with XELJANZ 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 and 4.8).

Hemoglobin

It is not recommended to initiate XELJANZ treatment in patients with low hemoglobin values (i.e., < 9 g/dL). Treatment with XELJANZ 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 and 4.8).

Lipids

Treatment with 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).

Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of XELJANZ 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 XELJANZ may be decreased to pretreatment levels with statin therapy.

Vaccinations

No data are available on the secondary transmission of infection by live vaccines to patients receiving XELJANZ. It is recommended that live vaccines not be given concurrently with XELJANZ. It is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating XELJANZ 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 ($\geq$ 4-fold increase in $\geq$ 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 ($\geq$ 2-fold increase in $\geq$ 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 $\geq$ 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 renal impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with moderate or severe renal impairment (see Section 4.2). In clinical trials, XELJANZ was not evaluated in patients with baseline creatinine clearance values (estimated by Cockroft-Gault equation) <40 mL/min (see Sections 4.2 and 5.2).

Patients with Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment (see Section 4.2). XELJANZ should not be used in patients with severe hepatic impairment (see Section 4.2). In clinical trials, XELJANZ was not evaluated in patients with severe hepatic impairment, or in patients with positive HBV or HCV serology.

Combination with Other RA Therapies

XELJANZ 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.

4.5 Interaction with other medicinal products and other forms of interactions

Interactions Affecting the Use of XELJANZ

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).

Tofacitinib exposure is decreased when co-administered with potent CYP inducers (e.g., rifampin). Potent CYP inducers (e.g., rifampin) may result in loss or reduced clinical response.

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).

Potential for XELJANZ 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 160 and 268 times the respective steady-state total and free C_{max} of a 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 535 and 893 times the steady-state total and free C_{max} of a 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 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 XELJANZ 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.

Immunosuppressive Drugs

Use of XELJANZ in combination with biologic DMARDs (e.g., abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab) or potent immunosuppressants, such as azathioprine and cyclosporine is not recommended.

Pediatric Population

Studies have only been performed in adults.

4.6 Pregnancy and lactation

There are no adequate and well-controlled studies on the use of XELJANZ 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). XELJANZ should not be used during pregnancy unless clearly necessary.

Women of reproductive potential should be advised to use effective contraception during treatment with XELJANZ and for at least 4 weeks after the last dose.

Tofacitinib was secreted in the milk of lactating rats (see Section 5.3). It is not known whether tofacitinib is secreted in human milk. Women should not breastfeed while treated with XELJANZ.

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

The following data includes 6 double-blind, controlled, multicenter studies of varying durations from 6-24 months (Studies I-VI, see Section 5.1). In these studies, 3200 patients were randomized and treated to doses of XELJANZ 5 mg twice daily (616 patients) or 10 mg twice daily (642 patients) monotherapy and 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 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 XELJANZ with a mean duration of 3.13 years, with 19405.8 patient-years of accumulated total drug exposure based on more than 8 years of continuous exposure to XELJANZ.

Safety information is also included for one large (N=4362), randomized 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 serious adverse reactions were serious infections (see Section 4.4).

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials (occurring in $\geq$ 2% of patients treated with 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 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 the table below are presented by System Organ Class (SOC) and frequency categories, defined using the following convention: very common ($\geq$ 1/10); common ($\geq$ 1/100 to < 1/10), uncommon ($\geq$ 1/1,000 to < 1/100) or rare ($\geq$ 1/10,000 to < 1/1,000). Within each frequency grouping, undesirable effects are presented in order of

decreasing seriousness.

ADRs BY SOC AND CIOMS FREQUENCY CATEGORY LISTED IN ORDER OF DECREASING MEDICAL SERIOUSNESS OR CLINICAL IMPORTANCE WITHIN EACH FREQUENCY CATEGORY AND SOC.

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

System Organ Class	Very Common ≥ 1/10	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 Sinusitis Bronchitis Nasopharyngitis Pharyngitis	Tuberculosis Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection	Sepsis Tuberculosis of central nervous system[b] Meningitis cryptococcal[b] Urosepsis Disseminated tuberculosis Necrotising fasciitis[b] Bacteraemia[b] Staphylococcal bacteraemia[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			Non-melanoma skin cancers[d]	

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000
(Including Cysts and Polyps)				
Blood and Lymphatic System Disorders		Anaemia	Leukopenia Lymphopenia Neutropenia	
Immune System Disorders			Drug hypersensitivity[e]	
Metabolism and Nutrition Disorders		Hyperlipidaemia	Dyslipidaemia Dehydration	
Psychiatric Disorders			Insomnia	
Nervous System Disorders		Headache	Paraesthesia	
Vascular Disorders		Hypertension	Venous thromboembolism[f]	
Respiratory, Thoracic and Mediastinal Disorders		Cough	Dyspnoea Sinus congestion	
Gastrointestinal Disorders		Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia		
Hepatobiliary Disorders			Hepatic steatosis	

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000
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 Oedema peripheral Fatigue		
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.

[a] The frequencies are based on pooled Phase 3 randomized clinical trial data.

[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.

System Organ Class	Very Common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000
[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). [g] Adverse Drug Reaction (ADR) identified post-marketing.				

Overall Infections

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) 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) 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 XELJANZ in the long-term safety all exposure population (total 4867 patients) was 46.1 patients with events per 100 patient-years (43.8 and 47.2 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).

Serious Infections

In the 6-month and 24-month, controlled clinical studies, the rate of serious infections in the 5 mg twice daily XELJANZ monotherapy group was 1.7 patients with events per 100 patient-years. In the 10 mg twice daily 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-month duration, the rates of serious infections in the 5 mg twice daily and 10 mg twice daily 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 XELJANZ groups, respectively. The most common serious infections reported with XELJANZ included pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis, and diverticulitis. Cases of opportunistic infections have been reported (see Section 4.4).

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 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).

Viral Reactivation

In 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).

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).

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). The safety experience in these patients was consistent with Studies I-V.

Laboratory Tests

Lymphocytes

In the controlled clinical studies, 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, 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).

Neutrophils

In the controlled clinical studies 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).

Liver Enzyme Tests

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 XELJANZ, or reduction in 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), ALT elevations > 3x ULN were observed in 1.65%, 0.41%, and 0% of patients receiving placebo, 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, XELJANZ 5 mg, and 10 mg twice daily, respectively.

In the Phase 3 monotherapy study (0-24 months) (Study VI, see Section 5.1), ALT elevations > 3x ULN were observed in 7.1%, 3.0%, and 3.0% of patients receiving methotrexate, 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, 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), ALT elevations > 3x ULN were observed in 0.9%, 1.24% and 1.14% of patients receiving placebo, XELJANZ 5 mg, and 10 mg twice daily, respectively. In these studies, AST elevations > 3x ULN were observed in 0.72%, 0.5% and 0.31% of patients receiving placebo,

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).

Lipids

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

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

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).

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

There is no experience with overdose of XELJANZ. There is no specific antidote for overdose with

XELJANZ. 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. 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 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 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 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 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 XELJANZ dosing in patients with rheumatoid arthritis were small, not dose-dependent and similar to those seen on placebo.

After treatment with 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 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.

<u>Mortality</u>

The IRs (95% CI) for all-cause mortality for XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ

10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all XELJANZ were 1.30 (0.29, 5.81), 3.45 (0.95, 12.54), and 2.34 (0.67, 8.16), respectively.

In other XELJANZ clinical studies, incidence rates for all-cause mortality in patients treated with XELJANZ 10 mg twice a day have not been higher than rates in patients treated with XELJANZ 5 mg twice a day. Mortality rates in patients treated with XELJANZ are similar to those reported for patients with RA treated with biologic therapies.

Infections

The IRs (95% CI) for all infections for XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all

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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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.

<u>Thromboembolism</u>

Venous Thromboembolism

The IRs (95% CI) for VTE for XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 $\geq$ 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 $\geq$ 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all XELJANZ were 1.12 (0.74, 1.70), 1.14 (0.75, 1.74), and 1.13 (0.78, 1.63), respectively.

<u>Major Adverse Cardiovascular Events (MACE), Including Myocardial Infarction</u>

MACE includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths excluding fatal pulmonary embolism. The IRs (95% CI) for MACE for XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all XELJANZ were

1.24 (0.81, 1.91), 1.43 (0.94, 2.18), and 1.33 (0.91, 1.94), respectively.

In the XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all 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 XELJANZ 5 mg

twice daily, XELJANZ 10 mg twice daily, and all 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 XELJANZ 5 mg twice daily treatment arm were 52.83, 6.01, and 1.68, respectively. The percentages for the XELJANZ 10 mg twice daily treatment arm were 54.46, 6.54, and 1.97, respectively. The percentages for all XELJANZ (combines XELJANZ 5 mg twice daily and 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 XELJANZ 5 mg twice daily treatment arm were 45.84, 3.21, and 0.98, respectively. The percentages for the XELJANZ 10 mg twice daily treatment arm were 51.58, 4.57, and 1.62, respectively. The percentages for all XELJANZ (combines XELJANZ 5 mg twice daily and 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 XELJANZ 5 mg twice daily, 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 XELJANZ 5 mg twice daily, 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

The efficacy and safety of 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). 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 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 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 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 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 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 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 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 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 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 XELJANZ-treated patients achieving ACR20, ACR50 and ACR70 responses in Studies I, II, IV, V and VI are shown in Table 5. In all studies, patients treated with either 5 or 10 mg twice daily 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 5), the difference from MTX in both tofacitinib groups, in achieving ACR20, ACR50 and ACR70 response rates was statistically significant at all timepoints ($p \leq 0.0001$). Tofacitinib, administered as monotherapy in MTX-naïve patients, significantly improved 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 XELJANZ at a dose of 10 mg twice daily generally had higher response rates compared to patients treated with 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 XELJANZ, 10 mg twice daily 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 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 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 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 XELJANZ (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 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 $\leqslant$ 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 5: Proportion of Patients with an ACR Response

Study I: DMARD Inadequate Responders				
Response Rate (%)	**Time**	**Placebo N=120**	**XELJANZ 5 mg Twice Daily Monotherapy N=241**	**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**	**XELJANZ 5 mg Twice Daily DMARD(s) N=311**	**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**	**XELJANZ 5 mg Twice Daily +MTX N=309**	**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**	**XELJANZ 5 mg Twice Daily +MTX N=132**	**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**	**XELJANZ 5 mg Twice Daily Monotherapy N=369**	**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 5. 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 6. Similar results were observed in Studies I, II and III.

Table 6: Components of ACR Response at Month 3 in Studies IV and V

Study IV: MTX Inadequate Responders				
Component	**Time**	**Placebo+MTX N=156**	**XELJANZ 5 mg Twice Daily +MTX N=316**	**XELJANZ 10 mg Twice Daily +MTX N=309**
Number of tender joints	Baseline	23	24	23

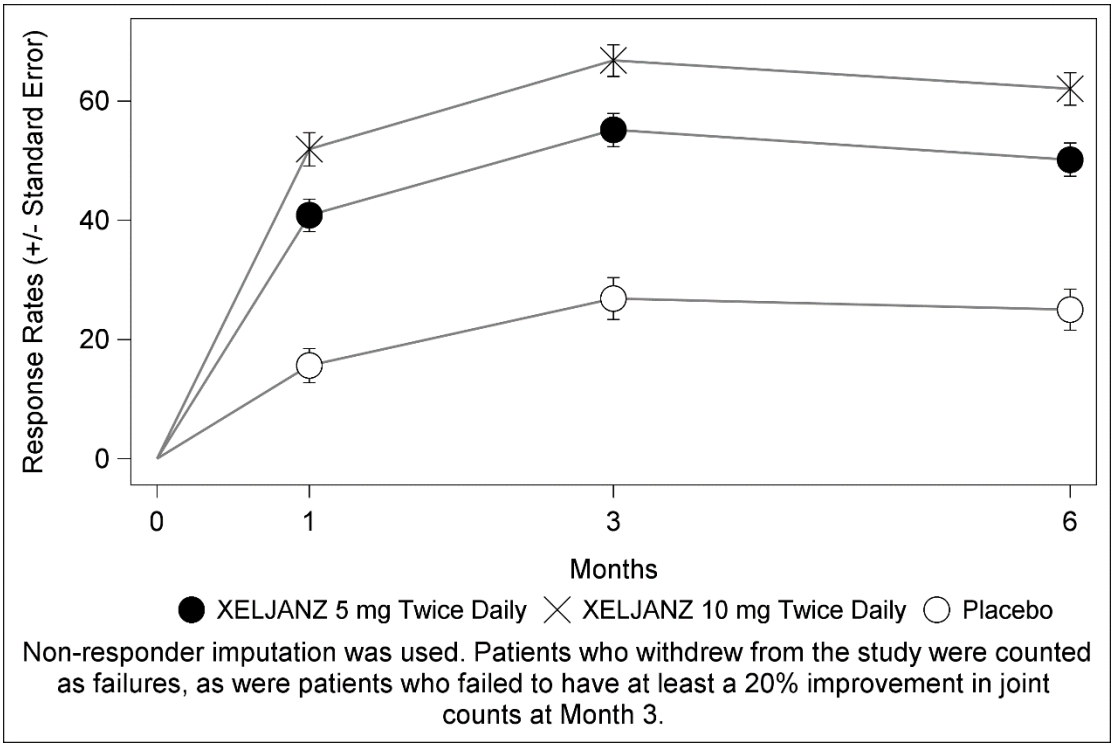
(0-68)	Month 3	18	13	10
Number of swollen joints (0-66)	Baseline	14	14	14
	Month 3	10	6	6
Pain[a]	Baseline	55	58	58
	Month 3	47	35	29
Patient global assessment[a]	Baseline	54	58	57
	Month 3	47	35	29
Disability index (HAQ-DI)[b]	Baseline	1.31	1.41	1.39
	Month 3	1.19	1.00	0.84
Physician global assessment[a]	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**	**XELJANZ 5 mg Twice Daily +MTX N=133**	**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 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, 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, 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 7.

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 XELJANZ 5 or 10 mg twice daily respectively, plus MTX, both significant vs. placebo plus MTX.

Table 7: Radiographic Changes at Months 6 and 12

	Study IV				
	Placebo + MTX N=139 Mean (SD)[a]	**XELJANZ 5 mg Twice Daily + MTX N=277 Mean (SD)[a]**	**XELJANZ 5 mg Twice Daily + MTX Mean Difference from Placebo[b] (CI)**	**XELJANZ 10 mg Twice Daily + MTX N=290 Mean (SD)[a]**	**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 XELJANZ minus placebo (95% CI = 95% confidence interval)

[c] Month 6 and Month 12 data are mean change from baseline

In Study VI, 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 8, 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 XELJANZ 5 or 10 mg twice daily respectively, both significant vs. MTX.

Table 8: Radiographic Changes at Months 6 and 12

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

[a] SD = Standard Deviation

[b] Difference between least squares means XELJANZ minus MTX (95% CI = 95% confidence interval)

	Study VI				
	MTX N=166 Mean (SD)[a]	**XELJANZ 5 mg Twice Daily N=346 Mean (SD)[a]**	**XELJANZ 5 mg Twice Daily Mean Difference from MTX[b] (CI)**	**XELJANZ 10 mg Twice Daily N=369 Mean (SD)[a]**	**XELJANZ 10 mg Twice Daily Mean Difference from MTX[b] (CI)**

[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 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). 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 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 XELJANZ 5 mg twice daily had similar decreases from baseline in HAQ-DI values and patients in the 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 9.

Table 9: Mean Change from Baseline in HAQ-DI

Study I: DMARD Inadequate Responders			
Time	**Placebo N=109**	**XELJANZ 5 mg Twice Daily Monotherapy N=237**	**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	**XELJANZ 5 mg Twice Daily +DMARD(s) N=292**	**XELJANZ 10 mg Twice Daily +DMARD(s) N=292**

Study I: DMARD Inadequate Responders				
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	**XELJANZ 5 mg Twice Daily +MTX N=188**	**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	**XELJANZ 5 mg Twice Daily +MTX N=294**	**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	**XELJANZ 5 mg Twice Daily +MTX N=117**	**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	**XELJANZ 5 mg Twice Daily Monotherapy N=355**	**XELJANZ 10 mg Twice Daily Monotherapy N=381**	
LS Mean Change in HAQ-DI at Month 3[a]	-0.47	-0.75**	-0.85**	

Study I: DMARD Inadequate Responders

[a] Primary efficacy time point.

[b] Statistical significance could not be declared in Study IV due to step-down procedure.

** p <0.0001, 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 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 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 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 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 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 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 XELJANZ-treated patients.

Improvement in productivity was evaluated using the Work Limitations Questionnaire (WLQ) scale at Month 3 in all studies. Patients receiving 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 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

The PK profile of tofacitinib 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.

Absorption and Distribution

Tofacitinib is well-absorbed, with an oral bioavailability of 74% following administration of XELJANZ. Co-administration of 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.

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 $\leq$ 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.

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 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). In patients with end-stage renal disease, the contribution of dialysis to the total clearance of tofacitinib was relatively small.

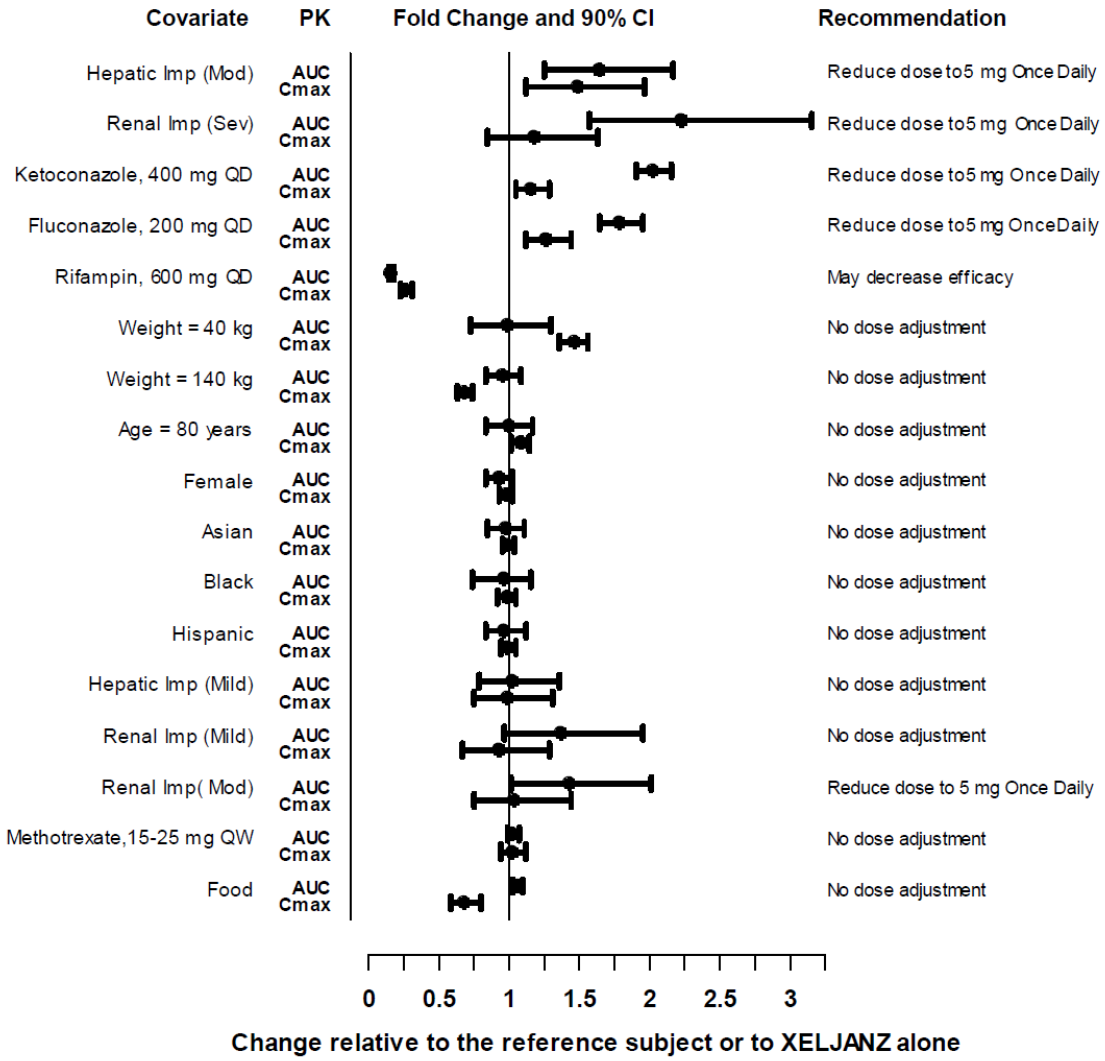
Hepatic Impairment

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).

Pediatric Population

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

Figure 2: Dosing Recommendation Based on Pharmacokinetic Data



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

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 hepatic 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 $\geq$ 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. Pharmaceutical Particulars

6.1 List of excipients

Microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate

Film Coat for 5 mg tablets: Opadry® II *White (33G28523):*
HPMC 2910/Hypromellose 6cP, titanium dioxide, lactose monohydrate, macrogol/PEG3350 triacetin (glycerol triacetate)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Please see details on the carton.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

HDPE bottles of 60 tablets with/without carton or blister (PVC/foil) of 10, 28 or 56 tablets in carton (1 blister of 10 tablets each; 2 or 4 blisters of 14 tablets each).

7. Marketing Authorization Holder

Pfizer (Thailand) Limited

8. Marketing Authorization Numbers

1C 35/58 (N)

9. Date of Authorization

27 December 2017

10. Date of Revision of the Text

15 September 2023