

AfME SmPC template Version 0.2, 09/2012
Rev. 0



Xeljanz[®]

Tofacitinib

5 mg film-coated tablets

CDS

AfME markets using same as LPD: Nigeria

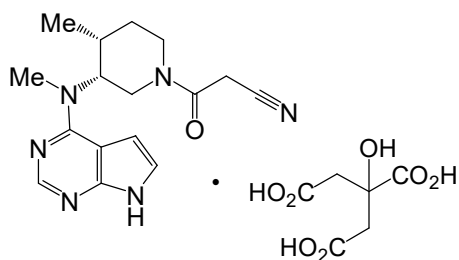
1. NAME OF THE MEDICINAL PRODUCT

XELJANZ® 5 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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:



Excipients with known effect:

Each XELJANZ 5 mg tablet also contains 62.567 mg lactose monohydrate.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

White round immediate release film-coated tablet (5 mg tablet)

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Rheumatoid Arthritis

XELJANZ is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).

4.2. Posology and method of administration

XELJANZ has not been studied and use should be avoided in combination with TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL23 antagonists, anti-integrins, selective co-stimulation modulators and

potent immunosuppressants such as azathioprine, cyclosporine, and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

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

Method of Administration

XELJANZ is given orally with or without food.

Rheumatoid Arthritis Posology

XELJANZ may be used as monotherapy or in combination with methotrexate (MTX) or other nonbiologic DMARDs.

The recommended dose of XELJANZ is 5 mg administered twice daily. Some patients may benefit from an increase to XELJANZ 10 mg administered twice daily based on clinical response.

Two XELJANZ 5 mg tablets are bioequivalent to one XELJANZ 10 mg tablet and may be used as an alternative to one XELJANZ 10 mg tablet.

In general, use the lowest effective dose to maintain therapeutic benefit.

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/mm³.

Table 1: Dose Adjustments for Lymphopenia

Low Lymphocyte Count [see Warnings and Precautions (Section 4.4)]	
Lab Value (cells/mm³)	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/mm³.

Table 2: Dose Adjustments for Neutropenia

Low Absolute Neutrophil Count (ANC) [see Warnings and Precautions (Section 4.4)]	
Lab Value (cells/mm³)	Recommendation
ANC > 1000	Maintain dose.
ANC 500-1000	For persistent decreases in this range, reduce XELJANZ dose or interrupt XELJANZ dosing until ANC is > 1000. For patients receiving XELJANZ 5 mg twice daily, interrupt XELJANZ dosing. When ANC is > 1000, resume XELJANZ 5 mg twice daily. For patients receiving XELJANZ 10 mg twice daily, reduce dose to XELJANZ 5 mg twice daily. When ANC is > 1000, increase to XELJANZ 10 mg twice daily based on clinical response.
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 less than 8.0 g/dL (Confirmed by repeat testing)	Interrupt the administration of XELJANZ until hemoglobin values have normalized.

Special Populations

Renal Impairment

If XELJANZ dose is 5 mg twice daily, the recommended dose in patients with severe renal impairment is XELJANZ 5 mg once daily (see Sections 4.4 and 5.2).

If XELJANZ dose is 10 mg twice daily, the recommended dose in patients with severe renal impairment is XELJANZ 5 mg twice daily (see Sections 4.4 and 5.2).

Rheumatoid Arthritis

No dose adjustment is required in patients with mild or moderate renal impairment. XELJANZ dosage should not exceed 5 mg twice daily in patients with 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. If XELJANZ dose is 5 mg twice daily, the recommended dose in patients with moderate hepatic impairment is XELJANZ 5 mg once daily.

If XELJANZ dose is 10 mg twice daily, the recommended dose in patients with moderate hepatic impairment is XELJANZ 5 mg twice daily.

Rheumatoid Arthritis

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 not exceed 5 mg twice daily in patients with moderate hepatic impairment (see Sections 4.4 and 5.2).

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

For indications with a maximum recommended dose of XELJANZ 5 mg twice daily in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole) or one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole), the recommended dose is XELJANZ 5 mg once daily.

Rheumatoid Arthritis

XELJANZ dosage should not exceed 5 mg twice daily in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole). XELJANZ dosage should not exceed 5 mg twice daily in patients receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

Rheumatoid Arthritis Patients Receiving Inducers of Cytochrome P450 (CYP3A4)

Coadministration of XELJANZ with potent CYP inducers (e.g., rifampin) may result in loss of or reduced clinical response (see Section 4.5). Coadministration of potent inducers of CYP3A4 with XELJANZ is not recommended.

Elderly Patients (≥65 years)

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

Pediatric

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

4.3. Contraindications

None

4.4. Special warnings and precautions for use

Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunomodulatory agents, including biologic DMARDs and 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 rheumatoid arthritis patients were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids which, in addition to rheumatoid arthritis may predispose them to infections. Other serious infections, that were not reported in clinical studies, may also occur (e.g., coccidioidomycosis).

In one large randomized post-authorization safety study (PASS) in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, a dose dependent increase in serious infections was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1). 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 elderly patients and in patients in whom other risk factors are identified (see Section 4.2). Urgently evaluate patients with signs and symptoms of VTE. Discontinue tofacitinib while evaluating suspected VTE, regardless of dose or indication.

Major Adverse Cardiovascular Events (including Myocardial Infarction)

In one large 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 older patients and in patients who were current or past smokers. Caution should be used in treating elderly patients, patients who are current or past smokers, and patients with other cardiovascular risk factors.

Malignancy and Lymphoproliferative Disorder [Excluding 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.

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.

Caution should be used in treating elderly patients, patients who are current or past smokers, and patients with other malignancy risk factors.

Recommendations for non-melanoma skin cancer are presented below.

Rheumatoid Arthritis

In controlled Phase 3 clinical studies in rheumatoid arthritis patients, 26 malignancies (excluding NMSC) including 5 lymphoma were diagnosed in 26 patients receiving 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 (3942 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 older patients and in patients who were current or past smokers.

Non-melanoma Skin Cancer

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. 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 (see Table 4 in Section 4.8).

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. Events were primarily reported as diverticular perforation, peritonitis, abdominal abscess and appendicitis. In the rheumatoid arthritis clinical trials, the incidence rate of gastrointestinal perforation across all studies (Phase 1, Phase 2, Phase 3 and long-term extension) for all treatments groups all doses was 0.11 events per 100 patient-years with XELJANZ therapy. Rheumatoid arthritis patients who developed gastrointestinal perforations were taking concomitant nonsteroidal 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. The incidence rate in the psoriasis clinical trials was 0.09 events/100 patient-years. The incidence rate in the psoriatic arthritis clinical trials (Phase 3 and long-term extension) was 0.13 patients with events per 100 patient-years with XELJANZ therapy.

In placebo-controlled induction studies for ulcerative colitis, gastrointestinal perforation (all cases) occurred in 2 (0.2%) patients treated with XELJANZ 10 mg twice daily and in 2 (0.9%) patients receiving placebo. In the Phase 3 maintenance study for ulcerative colitis, gastrointestinal perforation (all cases) was not reported in patients treated with XELJANZ and was reported in 1 patient treated with placebo.

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 and placebo were 2.11 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/mm³ 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/mm³). In patients who develop a confirmed absolute lymphocyte count <500 cells/mm³ 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/mm³) compared to placebo. It is not recommended to initiate XELJANZ treatment in patients with a low neutrophil count (i.e., ANC <1000 cells/mm³). For patients taking XELJANZ 10 mg twice daily who develop a persistent ANC of 500-1000 cells/mm³, reduce XELJANZ dose to 5 mg twice daily until ANC is >1000 cells/mm³. For patients taking XELJANZ 5 mg twice daily who develop a persistent ANC of 500-1000 cells/mm³, interrupt XELJANZ dosing until ANC is >1000 cells/mm³. In patients who develop a confirmed absolute neutrophil count <500 cells/mm³ 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 (≥ 4 -fold increase in ≥ 2 of 3 antigens) in the tofacitinib (57%) and placebo (62%) treatment groups. A modest reduction in the percentage of patients who achieved a satisfactory humoral response to pneumococcal polysaccharide vaccine (≥ 2 -fold increase in ≥ 6 of 12 serotypes) was observed in patients treated with tofacitinib monotherapy (62%) and methotrexate monotherapy (62%) as compared with placebo (77%), with a greater reduction in the response rate of patients receiving both tofacitinib and methotrexate (32%). The clinical significance of this is unknown.

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

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

In this study one patient experienced dissemination of the vaccine strain of varicella zoster virus, 16 days after vaccination. The patient was varicella virus naïve, as evidenced by no previous history of varicella infection and no anti-varicella antibodies at baseline. Tofacitinib was discontinued and the subject recovered after treatment with standard doses of antiviral

medication. Subsequent testing showed that this patient made robust anti-varicella T-cell and antibody responses to the vaccine approximately 6 weeks post-vaccination, but not at 2 weeks post-vaccination, as expected for a primary infection.

Patients with Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. XELJANZ dose should not exceed 5 mg twice daily in patients with severe renal impairment.

In clinical trials, XELJANZ was not evaluated in patients with baseline creatinine clearance values (estimated by Cockcroft-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 not exceed 5 mg twice daily in patients with moderate hepatic impairment.

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 Therapies

Rheumatoid Arthritis

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 interaction

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 coadministered 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 coadministered with potent CYP inducers (e.g., rifampin). Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to significantly alter the PK of tofacitinib.

Concomitant administration with methotrexate (15-25 mg MTX once weekly) had no effect on the PK of tofacitinib. Coadministration of ketoconazole, a strong CYP3A4 inhibitor, with a single dose of tofacitinib increased the AUC and C_{max} by 103% and 16%, respectively. Coadministration 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. Coadministration of tacrolimus (Tac), a mild inhibitor of CYP3A4, increased the AUC of tofacitinib by 21% and decreased the C_{max} of tofacitinib by 9%. Coadministration 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. Coadministration 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 80 times the steady state total C_{max} at 5 mg and 10 mg twice daily doses 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 coadministered with tofacitinib.

In vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug-metabolizing uridine 5'-diphospho-glucuronosyltransferases (UGTs), [UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7] at concentrations exceeding 250 times the steady state total C_{max} at 5 mg and 10 mg twice daily doses in rheumatoid arthritis patients.

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

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

Coadministration 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.

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

In rheumatoid arthritis patients the oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalize CYP enzyme activity in these patients. Therefore, coadministration with tofacitinib is not expected to result in clinically relevant increases in the metabolism of CYP substrates in RA patients.

Pediatric Population

Studies have only been performed in adults.

4.6. Fertility, pregnancy and lactation

There are no adequate and well-controlled studies on the use of 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/postnatal 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

Rheumatoid Arthritis

The following data includes 6 double-blind, controlled, multicenter studies of varying durations from 6-24 months (Studies I-VI, see Section 5.1). 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 19,405.8 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 post-authorization safety study (PASS) in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (CV risk factors defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g. nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations), and were on a stable background dose of methotrexate.

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.

Psoriatic Arthritis

XELJANZ 5 mg twice daily and 10 mg twice daily were studied in 2 double-blind Phase 3 clinical trials in patients with active psoriatic arthritis (PsA).

Study PsA-I had a duration of 12 months and included 422 patients who had an inadequate response to a csDMARD and who were naïve to treatment with a TNF-inhibitor (TNFi) biologic DMARD. Study PsA-I included a 3-month placebo-controlled period and also included adalimumab 40 mg subcutaneously once every 2 weeks for 12 months. Study PsA-II had a duration of 6 months and included 394 patients who had an inadequate response to at least one approved TNFi. Study PsA-II included a 3-month placebo-controlled period. All patients in the clinical trials were required to receive treatment with a stable dose of a csDMARD [the majority received methotrexate (78.2%)]. In the Phase 3 clinical trials, patients were randomized and treated with XELJANZ 5 mg twice daily (238 patients) or XELJANZ 10 mg twice daily (236 patients). The study population randomized and treated with XELJANZ (474 patients) included 45 (9.5%) patients aged 65 years or older and 66 (13.9%) patients with diabetes at baseline.

An additional long-term, open-label clinical trial was conducted which included 680 patients with psoriatic arthritis who originally participated in either of the 2 double-blind, controlled clinical trials. Patients who participated in this open-label clinical trial were initially treated with XELJANZ 5 mg twice daily. Starting at Month 1, escalation to XELJANZ 10 mg twice daily was permitted at investigator discretion; subsequent dose reduction to 5 mg twice daily was also permitted. This limits the interpretation of the long-term safety data with respect to dose.

Of the 783 patients (as of 10 May 2016) who received XELJANZ doses of 5 mg twice daily or 10 mg twice daily in psoriatic arthritis clinical trials, 665 received treatment for 6 months or longer, of whom 437 received treatment for one year or longer, of whom 44 received treatment for greater than or equal to 24 months.

Plaque Psoriasis

The following pooled data include one Phase 2 and four multicenter Phase 3 trials in psoriasis patients for a period of up to 56 weeks, including a 12-16 week placebo-controlled period. In the Phase 3 trials, patients received doses of 5 mg twice daily (1546 patients) or 10 mg twice daily (1549 patients). From the Phase 2 study, data on patients dosed at 5 mg twice daily (49 patients) and 15 mg twice daily (49 patients, integrated with the 10 mg twice daily group) were included in the safety analysis.

The long-term safety population includes all patients who participated in one of the double-blind, controlled trials and then participated in an ongoing long-term safety study. Patients who participated in the long-term safety study were initially treated with 10 mg twice daily for 3 months, and then modification of the XELJANZ dose was permitted. Therefore the ability to compare 5 and 10 mg twice daily is limited beyond the one year exposure in the Phase 3 studies.

Of the 3627 psoriasis patients (as of March 31, 2015) who received XELJANZ, doses of 5 mg twice daily or 10 mg twice daily, 2960 received treatment for greater than 6 months, 2479 received treatment for greater than one year, and 1742 received treatment for greater than 24 months.

Comparisons between placebo and XELJANZ were based on the first 12-16 weeks of exposure, and comparisons between XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily were based on the first 52-56 weeks of exposure.

All patients in these studies had moderate to severe chronic plaque psoriasis. The study population included 219 patients aged 65 years or older, 449 patients with diabetes and 149 Japanese patients (including 94 patients from a Japan local study).

Ulcerative Colitis

The following safety data were based on 4 randomized, double-blind, placebo-controlled studies: 2 Phase 3 induction studies of identical design (UC-I and UC-II), a Phase 3 maintenance study (UC-III), and 1 dose-ranging Phase 2 induction study (UC-V). Patients with moderately to severely active ulcerative colitis were enrolled in the Phase 2 and Phase 3 induction studies. In the induction studies, randomized patients received treatment with XELJANZ 10 mg twice daily (938 patients combined) or placebo (282 patients combined) for up to 8 weeks. Patients who completed either Study UC-I or Study UC-II and achieved clinical response entered Study UC-III. In Study UC-III, patients were re-randomized, such that 198 patients received XELJANZ 5 mg twice daily, 196 patients received XELJANZ 10 mg twice daily, and 198 patients received placebo for up to 52 weeks. Concomitant use of immunosuppressants or biologics was prohibited during these studies. Concomitant stable doses of oral corticosteroids were allowed in the induction studies, with taper of corticosteroids to discontinuation mandated within 15 weeks of entering the maintenance study. In addition to the induction and maintenance studies, long-term safety was evaluated in an open-label long-term extension study (Study UC-IV).

Clinical Trials Experience

The most common category of serious adverse reactions in rheumatoid arthritis, psoriatic arthritis and psoriasis was serious infections (see Section 4.4).

In induction and maintenance studies, across all treatment groups, the most common categories of serious adverse reactions in ulcerative colitis were gastrointestinal disorders and infections.

Rheumatoid Arthritis

In rheumatoid arthritis, 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 Table 4 are presented by System Organ Class (SOC). Within each SOC, undesirable effects are presented in order of decreasing seriousness.

Psoriatic Arthritis

In active psoriatic arthritis, the most commonly reported adverse reactions during the first 12 weeks in placebo controlled clinical trials (occurring in $\geq 2\%$ of patients treated with XELJANZ and at least 1% greater than the rate observed in patients on placebo) were bronchitis, diarrhea, dyspepsia, fatigue, headache, nasopharyngitis, pharyngitis.

The proportion of patients who discontinued treatment due to any adverse reactions during the first 12 weeks of the double-blind placebo controlled studies was 3.2% for XELJANZ treated patients and 2.5% for placebo-treated patients. The most common infection resulting in discontinuation of therapy was sinusitis.

Overall, the safety profile observed in patients with active psoriatic arthritis treated with XELJANZ was consistent with the safety profile in patients with rheumatoid arthritis.

Plaque Psoriasis

In psoriasis, the most commonly reported adverse reactions during the first 12-16 weeks in controlled clinical trials (occurring in $\geq 2\%$ of patients treated with XELJANZ and at least 1% greater than the rate observed in patients on placebo) were diarrhea, upper respiratory tract infections, blood creatine phosphokinase increased, blood cholesterol increased, hypercholesterolemia, hyperlipidemia, and headache.

The proportion of plaque psoriasis patients who discontinued treatment due to any adverse reaction during 0 to 12-16 weeks exposure in the double-blind, placebo-controlled trials was 3% for the patients taking XELJANZ and 4% for placebo-treated patients.

The most common infections resulting in discontinuation were pneumonia, urinary tract infection, and herpes zoster.

Ulcerative Colitis

The adverse reactions that occurred in at least 2% of patients receiving XELJANZ 10 mg twice daily and at least 1% greater than that observed in patients receiving placebo in the induction studies (Study UC I, Study UC II, and Study UC V) were increased blood creatine phosphokinase, nasopharyngitis, pyrexia, and headache.

In induction and maintenance studies, across all treatment groups, the most common categories of serious adverse reactions were gastrointestinal disorders and infections, and the most common serious adverse reaction was worsening of ulcerative colitis.

In the controlled clinical studies for ulcerative colitis, 1 case of breast cancer was reported in a placebo-treated patient and no cases of solid cancers or lymphoma were observed in XELJANZ treated patients. Malignancies have also been observed in the long term extension study in patients with ulcerative colitis treated with XELJANZ, including solid cancers and lymphoma.

In induction and maintenance studies, the most frequent reason for study discontinuation was worsening of ulcerative colitis. Excluding discontinuations due to worsening of ulcerative colitis, the proportion of patients who discontinued due to adverse reactions was less than 5% in any of the XELJANZ or placebo treatment groups in these studies.

Overall, the safety profile observed in patients with ulcerative colitis treated with XELJANZ was consistent with the safety profile of XELJANZ across indications.

The Adverse Drug Reactions (ADRs) listed in Table 4 are presented by System Organ Class (SOC). Within each SOC, undesirable effects are presented in order of decreasing seriousness.

Table 4. Adverse Drug Reactions for XELJANZ (RA, PsO, PsA, AS, UC and pcJIA Combined)

System Organ Class	Adverse Drug Reactions
Infections and infestations	Sepsis Tuberculosis of central nervous system Meningitis cryptococcal Urosepsis Disseminated tuberculosis Necrotizing fasciitis Bacteraemia Staphylococcal bacteraemia Tuberculosis <i>Pneumocystis jirovecii</i> pneumonia Pneumonia Pneumonia pneumococcal Pneumonia bacterial Diverticulitis Pyelonephritis Encephalitis Influenza Atypical mycobacterial infection <i>Mycobacterium avium</i> complex infection Cytomegalovirus infection Herpes zoster Cellulitis Arthritis bacterial Urinary tract infection Herpes simplex Sinusitis Bronchitis Gastroenteritis viral Nasopharyngitis Pharyngitis Viral infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Non-melanoma skin cancers
Blood and lymphatic system disorders	Leukopenia Lymphopenia Neutropenia Anaemia
Immune system disorders	Drug hypersensitivity*
Metabolism and nutrition disorders	Dyslipidaemia Hyperlipidaemia Dehydration
Psychiatric disorders	Insomnia

Table 4. Adverse Drug Reactions for XELJANZ (RA, PsO, PsA, AS, UC and pcJIA Combined)

System Organ Class	Adverse Drug Reactions
Nervous system disorders	Headache Paraesthesia
Vascular disorders	Venous thromboembolism** Hypertension
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough Sinus congestion
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia
Hepatobiliary disorders	Hepatic steatosis
Skin and subcutaneous tissue disorders	Rash Erythema Pruritus
Musculoskeletal and connective tissue disorders	Musculoskeletal pain Arthralgia Joint swelling Tendonitis
General disorders and administration site conditions	Pyrexia Oedema peripheral Fatigue
Investigations	Hepatic enzyme increased Transaminases increased Liver function test abnormal Gamma-glutamyltransferase increased Blood creatinine increased Blood cholesterol increased Low density lipoprotein increased Weight increased Blood creatine phosphokinase increased
Injury, poisoning and procedural complications	Ligament sprain Muscle strain

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

** Venous thromboembolism includes pulmonary embolism and deep vein thrombosis.

Overall infections

Rheumatoid Arthritis

In the 6-month and 24-month, controlled Phase 3 clinical studies the rates of infections in the 5 mg twice daily (total 616 patients) and 10 mg twice daily (total 642 patients) 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).

Psoriatic Arthritis

In the controlled Phase 3 studies of up to 6 month and up to 12 month, the frequency of infections in the XELJANZ 5 mg twice daily (238 patients) and XELJANZ 10 mg twice daily (236 patients) groups were 37.8% and 44.5%, respectively. The frequency of infections in the 3 month placebo controlled period was 23.5% for XELJANZ 5 mg twice daily (238 patients), 28.8% for XELJANZ 10 mg twice daily (236 patients) and 15.7% in the placebo group (236 patients).

The most commonly reported infections in the 3-month placebo-controlled period were nasopharyngitis (5.9% and 5.5% in the 5 mg twice daily and 10 mg twice daily dose groups, respectively) and upper respiratory tract infections (5.0% and 4.7% in the 5 mg twice daily and 10 mg twice daily dose groups, respectively).

As of May 2016, the overall rate of infections with XELJANZ in the long term safety population for combined doses was 63.5 patients with events per 100 patient-years.

Plaque Psoriasis

In the four placebo-controlled clinical trials, during 0 to 12-16 weeks exposure, the overall frequency of infections was 22% in the XELJANZ 5 mg twice daily group and 27% in the XELJANZ 10 mg twice daily group, and 23% in the placebo group. During 52-56 weeks of

double-blind exposure in three trials, the rate of infections in the 5 mg twice daily group was 35% and the rate in the 10 mg twice daily group was 43%.

The most commonly reported infections with XELJANZ during 0 to 12-16 weeks exposure were nasopharyngitis and upper respiratory infections (7% and 8% for nasopharyngitis in the 5 mg twice daily group and 10 mg twice daily group, respectively, and 4% and 5% for upper respiratory infections in the 5 mg twice daily group and 10 mg twice daily group, respectively). As of March 31, 2015, the overall rate of infections with XELJANZ in the long-term safety population for combined doses was 54.9 events per 100 patient-years.

Ulcerative Colitis

In the randomized 8 week Phase 2/3 induction studies, the proportions of patients with infections were 21.1% for XELJANZ 10 mg twice daily compared with 15.2% for placebo. In the randomized 52-week Phase 3 maintenance study, the proportion of patients with infections were 35.9% for XELJANZ 5 mg twice daily, 39.8% for XELJANZ 10 mg twice daily, and 24.2% for placebo. In the entire treatment experience with XELJANZ in the ulcerative colitis program, the overall incidence rate of infection was 65.7 events per 100 patient years (involving 47.9% of patients). The most common infection was nasopharyngitis, occurring in 16.8% of patients.

Serious Infections

Rheumatoid Arthritis

In the 6-month and 24-month, controlled clinical studies, the rate of serious infections in the 5 mg twice daily 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-months 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).

Psoriatic Arthritis

In the 6-month and 12-month Phase 3 studies, the rate of serious infections in the XELJANZ 5 mg twice daily group was 1.30 patients with events per 100 patient-years. In the XELJANZ 10 mg twice daily group, the rate was 2.0 patients with events per 100 patient-years. In the long-term safety population, the overall rate of serious infections was 1.4 patients with events per 100 patient-years for XELJANZ treated patients. The most common serious infection reported with XELJANZ was pneumonia.

Plaque Psoriasis

In the four placebo-controlled clinical studies, during the initial 12-16 weeks of placebo-controlled exposure, serious infections were reported in 5 patients (1.7 events/100 patient-years) who received 5 mg twice daily of XELJANZ, 4 patients (1.3 events/100 patient-years) who received 10 mg twice daily of XELJANZ, and in 2 patients (1.5 events/100 patient-years) who received placebo twice daily.

During 52-56 weeks of double-blind exposure in three trials, serious infections were reported in 11 patients (1.4 events/100 patient-years) who received 5 mg twice daily of XELJANZ and 21 patients (2.4 events/100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 1.05 (-0.28, 2.38) events per 100 patient-years for 10 mg twice daily XELJANZ compared to 5 mg twice daily XELJANZ.

In a controlled clinical study of 12 weeks duration, where etanercept was used as an active comparator, rates of serious infections were 0.6% for each active treatment arm: XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily and etanercept 50 mg twice weekly.

In the long-term safety population, the overall rate of serious infections was 1.6 events per 100 patient-years for XELJANZ treated patients. The most common serious infections reported with XELJANZ included pneumonia, herpes zoster, and appendicitis.

At both doses, the rate of serious infections was higher in patients aged 65 years or greater and in patients with diabetes.

Ulcerative Colitis

In the randomized 8-week Phase 2/3 induction studies, the proportion of patients with serious infections in patients treated with XELJANZ 10 mg twice daily was 0.9% (8 patients) compared with 0.0% in patients treated with placebo. In the randomized 52-week Phase 3 maintenance study, the incidence rates of serious infections in patients treated with XELJANZ 5 mg twice daily (1.35 events per 100 patient-year) and in patients treated with XELJANZ 10 mg twice daily (0.64 events per 100 patient-year) were not higher than that for placebo (1.94 events per

100 patient-year). The incidence rate of serious infections in the entire treatment experience with XELJANZ in patients with ulcerative colitis was 2.05 events per 100 patient-year. There was no apparent clustering into specific types of serious infections.

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.

Psoriasis

In the 12 to 16 week placebo period of completed randomized controlled studies of 12 to 56 weeks 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, 0.96), 0.00 (0.00, 0.95), and 0.00 (0.00, 2.09) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.00 (0.00, 0.96), 0.00 (0.00, 0.95), and 0.00 (0.00, 2.09) patients with events per 100 PYs respectively.

In the full randomized period of completed controlled studies of 52 to 56 weeks duration, the IRs (95% CI) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily for PE were 0.00 (0.00, 0.41) and 0.00 (0.00, 0.38) patients with events per 100 PYs respectively; the IRs (95%

CI) for DVT were 0.00 (0.00, 0.41) and 0.00 (0.00, 0.38) 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 study, the IRs (95% CI) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily for PE were 0.13 (0.02, 0.47) and 0.09 (0.04, 0.19) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.06 (0.00, 0.36) and 0.06 (0.02, 0.15) patients with events per 100 PYs respectively.

Psoriatic arthritis

In the 3 month placebo period of completed randomized controlled studies of 6 to 12 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, 6.75), 0.00 (0.00, 6.78), and 0.00 (0.00, 6.87) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.00 (0.00, 6.75), 0.00 (0.00, 6.78), and 0.00 (0.00, 6.87) patients with events per 100 PYs respectively.

In the full randomized period of completed controlled studies of 6 to 12 months, the IRs (95% CI) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily for PE were 0.00 (0.00, 1.83) and 0.00 (0.00, 1.87) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.00 (0.00, 1.83) and 0.51(0.01, 2.83) patients with events per 100 PYs respectively.

In the long term safety population that includes exposure during completed randomized controlled studies and ongoing open label long-term extension study, the IRs (95% CI) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily for PE were 0.11 (0.00, 0.60) and 0.00 (0.00, 0.58) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.00 (0.00, 0.40) and 0.16 (0.00, 0.87) patients with events per 100 PYs respectively.

Ulcerative Colitis

In the completed randomized placebo-controlled induction studies of 8 weeks duration, the IR (95% CI) for tofacitinib 10 mg twice daily and placebo for PE were 0.00 (0.00, 2.22) and 1.98 (0.05, 11.04) patients with events per 100 PYs; the IR (95% CI) for DVT were 0.00 (0.00, 2.22) and 1.99 (0.05, 11.07) patients with events per 100 PYs respectively.

In the completed randomized maintenance study of 52 weeks duration, the IRs (95% CI) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily for PE were 0.00 (0.00, 2.48) and 0.00 (0.00, 2.35) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.00 (0.00, 2.48) and 0.00 (0.00, 2.35) patients with events per 100 PYs respectively.

In the long term safety population that includes exposure during completed randomized controlled studies and ongoing open label long-term extension study, the IRs (95% CI) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily for PE were 0.00 (0.00, 0.54) and 0.20 (0.05, 0.52) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.00 (0.00, 0.54) and 0.05 (0.00, 0.28) 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

In the clinical trials in psoriatic arthritis and ulcerative colitis, changes in lymphocytes, neutrophils, and lipids observed with XELJANZ treatment were similar to the changes observed in clinical trials in rheumatoid arthritis.

In the clinical trials in psoriatic arthritis and ulcerative colitis, changes in liver enzyme tests observed with XELJANZ treatment were similar to the changes observed in clinical trials in rheumatoid arthritis where patients received background DMARDs.

Rheumatoid Arthritis

Lymphocytes

In the controlled clinical studies in rheumatoid arthritis, confirmed decreases in lymphocyte counts below 500 cells/mm³ occurred in 0.23% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. In the controlled clinical trials in psoriasis, confirmed decreases in absolute lymphocyte count below 500 cells/mm³ occurred in 3 patients (0.1%) for XELJANZ and none in placebo, during the first 0 to 12-16 weeks of exposure.

In the long-term safety population in rheumatoid arthritis, confirmed decreases in lymphocyte counts below 500 cells/mm³ occurred in 1.3% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. In the long-term safety population in psoriasis, confirmed decreases in lymphocyte counts below 500 cells/mm³ occurred in 0.7% of patients for the combined dose groups.

Confirmed lymphocyte counts <500 cells/mm³ were associated with an increased incidence of treated and serious infections (see Section 4.4).

Neutrophils

In the controlled clinical studies in rheumatoid arthritis, confirmed decreases in ANC below 1000 cells/mm³ occurred in 0.08% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. In the controlled clinical trials for psoriasis, no patients had confirmed neutrophil levels below 1000 cells/mm³ in either of the XELJANZ treatment groups or placebo group during the first 0 to 12-16 weeks of exposure. There were no confirmed decreases in ANC below 500 cells/mm³ 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

Rheumatoid Arthritis

Confirmed increases in liver enzymes >3 times the upper limit of normal (3x ULN) were uncommonly observed. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of 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%, 0.50% 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).

Plaque Psoriasis

In the controlled clinical trials, during 0 to 12-16 weeks exposure, ALT elevations greater than or equal to 3x ULN were observed in 0%, 0.4%, and 1.0%, of patients receiving placebo, 5 mg twice daily, and 10 mg twice daily, respectively. In these trials, AST elevations greater than or equal to 3x ULN were observed in 0.2%, 0.1%, and 0.2% of patients receiving placebo, 5 mg twice daily, and 10 mg twice daily, respectively. In studies of 52-56 weeks of duration, changes in AST and ALT appeared to be consistent over time.

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 of rheumatoid arthritis and psoriasis. Increases were observed at this time point and remained stable thereafter.

Rheumatoid Arthritis

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

- Mean LDL cholesterol increased by 15% in the 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.

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).

Plaque Psoriasis

Changes in lipid parameters from baseline through the end of the study (52-56 weeks) in the controlled clinical studies of psoriasis are summarized below:

- Mean LDL cholesterol increased by 9.3% in the XELJANZ 5 mg twice daily arm and 14.4% in the XELJANZ 10 mg twice daily arm.
- Mean HDL cholesterol increased by 11.7% in the XELJANZ 5 mg twice daily arm and 15.4% in the XELJANZ 10 mg twice daily arm.

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

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

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

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

4.9. Overdose

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.

Mortality

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 XELJANZ clinical studies that included 10 mg twice a day, 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, PsO, PsA, AS, pcJIA, and UC, 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.

Thromboembolism

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.

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 $\geq 2 \times$ ULN at 12 months treatment versus those with D-dimer level $< 2 \times$ 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 $\geq 2 \times$ 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.

Major Adverse Cardiovascular Events (MACE), Including Myocardial Infarction

MACE includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths excluding fatal pulmonary embolism. The IRs (95% CI) for MACE for 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

Rheumatoid Arthritis

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 (nonbiologic 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 nonbiologic 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, nonresponding 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 ≤ 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

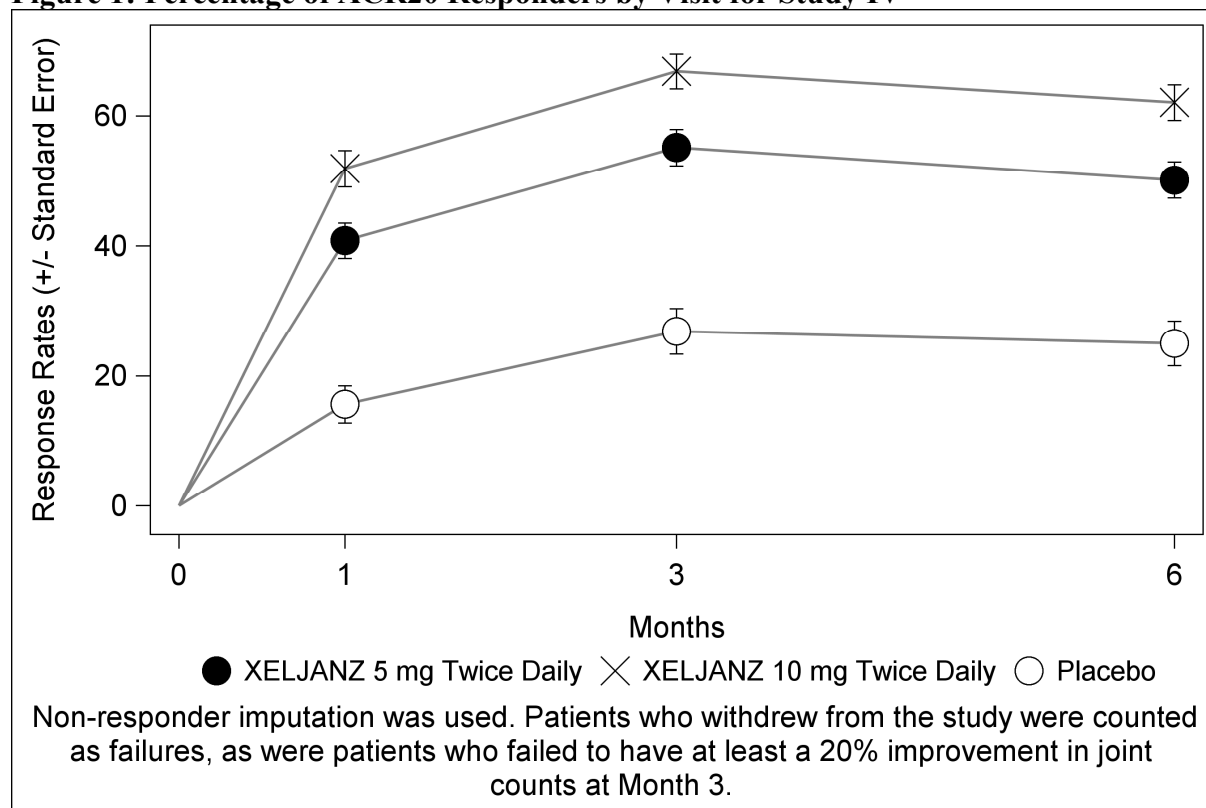
Study IV: MTX Inadequate Responders				
Component	Time	Placebo + MTX N=156	XELJANZ 5 mg Twice Daily+ MTX N=316	XELJANZ 10 mg Twice Daily + MTX N=309
Number of tender joints (0-68)	Baseline	23	24	23
	Month 3	18	13	10
Number of swollen joints (0-66)	Baseline	14	14	14
	Month 3	10	6	6
Pain ^a	Baseline	55	58	58
	Month 3	47	35	29
Patient global assessment ^a	Baseline	54	58	57
	Month 3	47	35	29
Disability index (HAQ-DI) ^b	Baseline	1.31	1.41	1.39
	Month 3	1.19	1.00	0.84
Physician global assessment ^a	Baseline	56	59	58
	Month 3	43	30	25
CRP (mg/L)	Baseline	13.7	15.5	17.0
	Month 3	14.6	6.9	4.4
Study V: TNF Inhibitor Inadequate Responders				
Component	Time	Placebo + MTX N=132	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)

^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 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 monotherapy Twice Daily 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) 1. N=147	XELJANZ 5 mg Twice Daily + DMARD(s) N=292	XELJANZ 10 mg Twice Daily + DMARD(s) N=292	
LS Mean Change in HAQ-DI at Month 3 ^a	-0.21	-0.46**	-0.56**	
Study III: MTX Inadequate Responders				
	Placebo + MTX N=98	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**	

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

Absorption and Distribution

Tofacitinib is well-absorbed, with an oral bioavailability of 74% following administration of XELJANZ. Coadministration 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 α 1-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 6.

Modifications required for special populations are described in Section 4.2.

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.

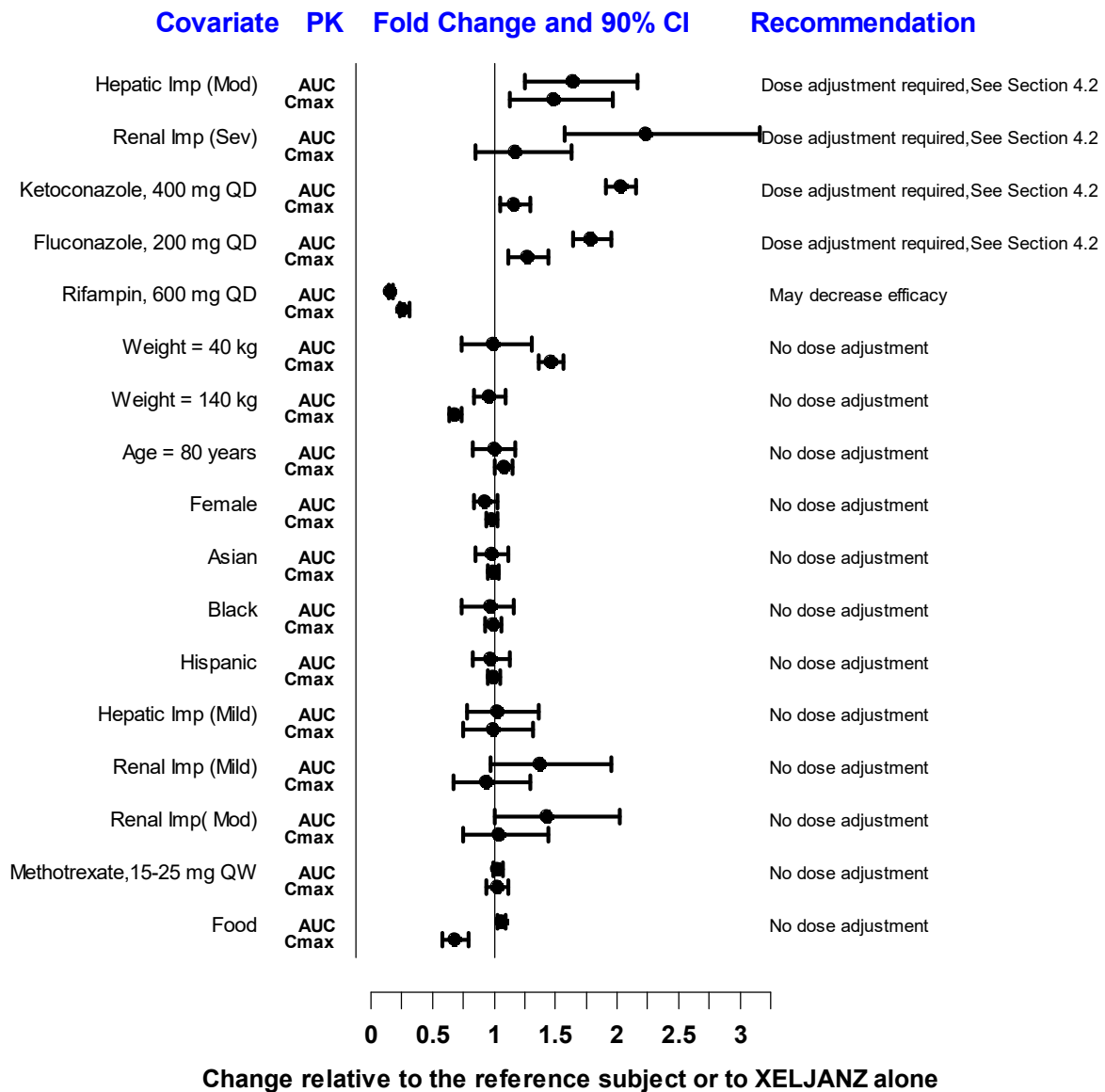
Hepatic Impairment

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 6: XELJANZ Dosing Recommendation Based on Pharmacokinetic Data



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

Note: Reference groups for renal and hepatic impairment data are subjects with normal renal or hepatic function, respectively; reference group for drug interaction and food effect studies is administration of XELJANZ alone:

Mod=moderate; Sev=severe; Imp=impairment

*Dose adjustment required for special populations are described in Section 4.2.

5.3. Nonclinical safety data

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

Lymphoma was observed in 3 of 8 adult and 0 of 14 juvenile monkeys dosed with tofacitinib at 5 mg/kg twice daily. The no observed adverse effect level (NOAEL) for the lymphomas was 1 mg/kg twice daily. The unbound AUC at 1 mg/kg twice daily was 341 ng•h/mL, which is approximately half of the unbound AUC at 10 mg twice daily and similar to the unbound AUC at 5 mg twice daily in humans.

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

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib was not carcinogenic in mice up to a high dose of 200 mg/kg/day (unbound drug AUC of ~19-fold the human AUC at 10 mg twice daily). Benign Leydig cell tumors were observed in rats: benign Leydig cell tumors in rats are not associated with a risk of Leydig cell tumors in humans. Hibernomas (malignancy of brown adipose tissue) were observed in female rats at doses \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/postnatal development. Tofacitinib had no effects on male fertility, sperm motility, or sperm concentration. Tofacitinib was secreted in milk of lactating rats.

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) containing:

Microcrystalline Cellulose
Lactose Monohydrate
Croscarmellose Sodium
Magnesium Stearate

6.2. Incompatibilities

Not applicable

6.3. Shelf life

Keep out of the sight and reach of children.

Do not use XELJANZ after the expiry date which is stated on the Carton/Bottle Label after EXP:. The expiry date refers to the last day of that month.

6.4. Special precautions for storage

Store below 30°C.

This medicinal product does not require any special temperature or light storage conditions. Store in the original package.

6.5. Nature and contents of container

XELJANZ: HDPE bottles with desiccant and child-resistant caps containing 60 film-coated tablets.

6.6. Special precautions for disposal and other handling

No special requirements.

7. FURTHER INFORMATION

MANUFACTURED BY

Pfizer Manufacturing Deutschland GmbH,
Betriebsstätte Freiburg,
Mooswaldallee 1, D-79090
Freiburg, Germany.

8. PRESCRIPTION STATUS

Prescription Only Medicine

9. DATE OF REVISION OF THE TEXT

July 2021

Document Approval Record

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Document Title:

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Signed By:

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