PRODUCT MONOGRAPH

PrXELJANZ®
tofacitinib, tablets, oral
5 mg tofacitinib (as tofacitinib citrate)
10 mg tofacitinib (as tofacitinib citrate)

PrXELJANZ® XR
tofacitinib extended-release, tablets, oral
11 mg tofacitinib (as tofacitinib citrate)

ATC Code: L04AA29
Selective Immunosuppressant

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PrXELJANZ®
PrXELJANZ® XR
Tofacitinib tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tofacitinib tablets / 5 mg tofacitinib and 10 mg (as tofacitinib citrate) Tofacitinib extended-release tablets / 11 mg tofacitinib (as tofacitinib citrate)	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Rheumatoid Arthritis
XELJANZ/XELJANZ XR (tofacitinib), in combination with methotrexate (MTX), is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA) in adult patients with moderately to severely active RA who have had an inadequate response to MTX.

In cases of intolerance to MTX, physicians may consider the use of XELJANZ/XELJANZ XR (tofacitinib) as monotherapy.

Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biological disease-modifying anti-rheumatic drugs (bDMARDs) or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Psoriatic Arthritis
XELJANZ (tofacitinib), in combination with methotrexate (MTX) or another conventional synthetic disease-modifying antirheumatic drug (DMARD), is indicated for reducing the signs and symptoms of psoriatic arthritis (PsA) in adult patients with active PsA when the response to previous DMARD therapy has been inadequate.

Limitations of Use: Use of XELJANZ in combination with biological disease-modifying anti-rheumatic drugs (bDMARDs) or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ulcerative Colitis
XELJANZ (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) with an inadequate response, loss of response or intolerance to either conventional UC therapy or a TNFα inhibitor.

Limitations of Use: Use of XELJANZ in combination with biological UC therapies or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Pediatrics (<18 years of age)
The safety and effectiveness of XELJANZ/XELJANZ XR in pediatric patients have not been established. Therefore, XELJANZ/XELJANZ XR should not be used in this patient population (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Geriatrics (>65 years of age)
The frequency of serious infection among XELJANZ treated subjects 65 years of age and older was higher than among those under the age of 65. Therefore, caution should be used when treating the elderly with XELJANZ/XELJANZ XR (see **WARNINGS AND PRECAUTIONS**, **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

CONTRAINDICATIONS

XELJANZ/XELJANZ XR (tofacitinib) is contraindicated:

- In patients with known hypersensitivity to tofacitinib or any of its components. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- In patients with severe hepatic impairment.
- During pregnancy and breastfeeding.

WARNINGS AND PRECAUTIONS

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with XELJANZ/XELJANZ XR (tofacitinib) are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR use.**
- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized disease.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Treatment with XELJANZ/XELJANZ XR should not be initiated in patients with active infections including chronic or localized infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy (see ADVERSE REACTIONS).

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications (see WARNINGS AND PRECAUTIONS).

THROMBOSIS
Rheumatoid arthritis patients with at least one cardiovascular (CV) risk factor had a higher rate of all-cause mortality and thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, with XELJANZ 10 mg twice daily compared to those treated with 5 mg twice daily or TNF blockers. Many of these adverse events were serious and some resulted in death. Avoid XELJANZ/XELJANZ XR in patients at risk of thrombosis. Discontinue XELJANZ/XELJANZ XR and promptly evaluate patients with symptoms of thrombosis (see WARNINGS AND PRECAUTIONS, Cardiovascular).

For patients with ulcerative colitis (UC), use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response (see DOSAGE AND ADMINISTRATION).

General

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

Cardiovascular

Heart Rate Decrease and PR Interval Prolongation: XELJANZ caused a decrease in heart rate and a prolongation of the PR interval (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests** and **ADVERSE REACTIONS**). Caution should be observed in patients with a low heart rate at baseline (<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Concomitant medications that result in a decrease in heart rate and/or PR interval prolongation should be avoided to the extent possible during treatment with XELJANZ/XELJANZ XR (see **DRUG INTERACTIONS**).

Thrombosis

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, was observed at an increased incidence in patients treated with XELJANZ in a large, ongoing post-marketing study. Rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular (CV) risk factor treated with XELJANZ 10 mg twice a day had a higher rate of all-cause mortality, including sudden CV death, and thrombosis compared to those treated with XELJANZ 5 mg given twice daily or TNF blockers. Many of these events were serious and some resulted in death (see **SERIOUS WARNINGS AND PRECAUTIONS BOX**).

In a long-term extension study in patients with ulcerative colitis (UC), four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one death in a patient with advanced cancer.

A dosage of XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily is not recommended for the treatment of RA or psoriatic arthritis (PsA) (see **DOSAGE AND ADMINISTRATION**).

For the treatment of UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response (see **DOSAGE AND ADMINISTRATION**).

Avoid XELJANZ/XELJANZ XR in patients that may be at increased risk of thrombosis. Discontinue XELJANZ/XELJANZ XR and promptly evaluate patients with symptoms of thrombosis."

Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported with XELJANZ in rheumatoid arthritis patients, although the role of JAK inhibition in these events is not known. Many patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. The relative contribution of these concomitant medications versus XELJANZ to the development of gastrointestinal perforations is not known.

There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ arms in clinical trials of patients with ulcerative colitis (UC), and many of them were receiving background corticosteroids.

XELJANZ/XELJANZ XR should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., use of concomitant NSAIDs and/or corticosteroids, patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation (see **ADVERSE REACTIONS**).

Hepatic/Biliary/Pancreatic

XELJANZ/XELJANZ XR is contraindicated in patients with severe hepatic impairment.

Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo (see **WARNINGS AND PRECAUTIONS – Laboratory parameters** and **ADVERSE REACTIONS**).

Evaluate liver enzymes before initiating XELJANZ and thereafter according to routine patient management (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**). Prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury (DILI). If increases in ALT (alanine transaminase) or AST (aspartate transaminase) are observed and DILI is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until the diagnosis is excluded.

Most of the liver enzyme abnormalities in RA and PsA patients occurred in studies with background DMARD (primarily methotrexate) therapy.

One case of DILI was reported in a RA patient treated with tofacitinib 10 mg BID for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT with values greater than 3x ULN associated concurrently with total bilirubin value greater than 2x ULN, which required hospitalization and a liver biopsy.

In UC patients, XELJANZ treatment with 5 and 10 mg BID was also associated with an increased incidence of liver enzyme elevation compared to placebo, with a trend for higher incidence with the 10 mg BID as compared to the 5 mg BID (see **WARNINGS AND PRECAUTIONS – Laboratory parameters** and **ADVERSE REACTIONS**).

The impact of XELJANZ/XELJANZ XR on chronic viral hepatitis reactivation is unknown. XELJANZ/XELJANZ XR has not been studied in patients with positive hepatitis B virus or hepatitis C virus serology, and should therefore not be used in these populations.

XELJANZ/XELJANZ XR has not been studied in patients with severe hepatic impairment, and should not be used in these patients. XELJANZ XR should not be used in patients with moderate to severe hepatic impairment. Dose adjustment of XELJANZ is recommended for patients with moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Immune

Hypersensitivity Reactions: Reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients treated with XELJANZ/XELJANZ XR. Some events were serious. If a hypersensitivity reaction is suspected, promptly discontinue tofacitinib while evaluating the potential cause or causes of the reaction (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

Immunocompromised Patients: XELJANZ/XELJANZ XR can increase the risk of infections and immunosuppression when co-administered with potent immunosuppressants such as cyclosporine, azathioprine and tacrolimus. Combined use of XELJANZ/XELJANZ XR with potent immunosuppressive drugs has not been studied and is not recommended (see **DRUG INTERACTIONS**).

Immunizations

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

In patients being considered for XELJANZ/XELJANZ XR therapy, live zoster vaccine 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 XELJANZ/XELJANZ XR.

In a clinical trial, a varicella naïve patient treated with XELJANZ and methotrexate developed disseminated infection with the vaccine strain of the varicella zoster virus 16 days after vaccination. A satisfactory immune response to the vaccine was developed 6 weeks post-vaccination.

In a randomized, double-blind, placebo-controlled study in 200 adult RA patients treated with XELJANZ 10 mg BID or placebo, humoral responses to concomitant pneumococcal and influenza vaccines were assessed. The percentages of patients achieving a satisfactory humoral response to pneumococcal vaccines were lower for the XELJANZ group than the placebo group. This effect was more pronounced for patients receiving background methotrexate. A total of 31.6% XELJANZ-treated subjects and 61.8% placebo-treated subjects who received background

methotrexate achieved a ≥2-fold increase in antibody concentrations to ≥6 of 12 pneumococcal antigens.

In the same study, the proportion of patients achieving protective antibody levels to the influenza antigens was lower in the XELJANZ group (64.9%) compared to the placebo group (92.7%) in patients receiving background methotrexate. However, the difference in humoral response to the influenza vaccine was small with 50.9% of patients in the XELJANZ group and 58.2% in the placebo group with background methotrexate achieving a ≥4-fold increase in antibody titers to ≥2 of 3 influenza antigens.

Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in rheumatoid arthritis patients receiving immunomodulatory agents, including biologic DMARDs and XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcus, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infections, and listeriosis were reported with XELJANZ (see **ADVERSE REACTIONS**). Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

Patients treated with XELJANZ 10 mg BID are at higher risk of serious infections, and herpes zoster infections compared to those treated with 5 mg BID. The incidence rate per 100 person-years (PYs) for herpes zoster opportunistic infections in the UC 52-week maintenance study was higher in patients treated with XELJANZ 10 mg BID (6.64) as compared to XELJANZ 5 mg BID (2.05) or placebo (0.97) (see **ADVERSE REACTIONS**).

XELJANZ/XELJANZ XR should not be administered in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating XELJANZ/XELJANZ XR in patients:

- with chronic or recurrent infections,
- who have been exposed to tuberculosis,
- with a history of a serious or an opportunistic infection,
- who have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or
- with 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 XR. XELJANZ/XELJANZ XR should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ/XELJANZ XR should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. 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 RA patients treated with XELJANZ in clinical trials and in the post-marketing setting.

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.

For discontinuation and monitoring criteria for lymphopenia see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**.

Treatment with XELJANZ was associated with increased rates of infections in Asian patients compared to other races (see **WARNINGS AND PRECAUTIONS – Special Populations** and **ADVERSE REACTIONS**). XELJANZ/XELJANZ XR should be used with caution in this population.

Tuberculosis
Patients should be evaluated and tested for latent or active infection prior to administration of XELJANZ/XELJANZ XR and periodically (e.g. annually) while taking XELJANZ/XELJANZ XR.

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.

Antituberculosis therapy should also be considered prior to administration of XELJANZ/XELJANZ XR in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but have risk factors for tuberculosis infection.

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

Viral Reactivation
Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. Post-marketing cases of hepatitis B reactivation have been reported in patients treated with XELJANZ (see **ADVERSE REACTIONS**). The impact of XELJANZ/XELJANZ XR on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ/XELJANZ XR.

Laboratory Parameters
Lymphopenia: Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections.

Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3). In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3, XELJANZ/XELJANZ XR should be discontinued.

For recommended monitoring and dose modifications based on lymphocyte counts see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests** and **DOSAGE AND ADMINISTRATION**.

Neutropenia: Treatment with XELJANZ was associated with an increased incidence of neutropenia (<2000/mm^3) compared to placebo.

Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a low neutrophil count (i.e., ANC (absolute neutrophil count) <1000/mm^3). For patients who develop a persistent ANC of 500-1000/mm^3, interrupt dosing until ANC is >1000 cells/mm^3. In patients who develop an absolute neutrophil count <500 cells/mm^3, discontinue treatment.

For recommended monitoring and dose modification based on ANC, see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests** and **DOSAGE AND ADMINISTRATION**.

Anemia: Treatment with tofacitinib has been associated with decreases in hemoglobin levels. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with low hemoglobin values (i.e., <9 g/dL). Treatment with XELJANZ/XELJANZ XR should be interrupted in patients who develop hemoglobin levels <8 g/dL or whose hemoglobin level drops >2 g/dL on treatment.

For recommended monitoring and dose modification based on hemoglobin results, see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests** and **DOSAGE AND ADMINISTRATION**.

Liver Enzyme Elevations: Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo (see **WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic**, and **ADVERSE REACTIONS**). Most of these abnormalities in RA and PsA patients occurred in studies with background DMARD (primarily methotrexate) therapy.

In UC patients, XELJANZ treatment with 5 and 10 mg BID was also associated with an increased incidence of liver enzyme elevation compared to placebo, with a trend for higher incidence with the 10 mg BID dose as compared to the 5 mg BID dose.

One patient treated with XELJANZ 10 mg BID in the maintenance UC study experienced an increase in liver enzymes which decreased upon discontinuation of treatment. The case was adjudicated as possible DILI, while noting ultrasound findings of fatty liver.

Routine monitoring of liver enzymes and prompt investigation of the cause of liver enzyme elevations is recommended to identify potential cases of DILI (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**).

Lipid Elevations: Treatment with XELJANZ was associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (see **ADVERSE REACTIONS**).

Maximum effects were generally observed within 6 weeks. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed at baseline and approximately 4-8 weeks following initiation of XELJANZ/XELJANZ XR therapy, and every 6 months thereafter (see **WARNINGS AND PRECAUTIONS – Monitoring and Laboratory Tests**). Patients should be managed according to local clinical guidelines for the management of hyperlipidemia.

Malignancies and Lymphoproliferative Disorder

Malignancies have been observed in patients treated with XELJANZ. In patients treated with XELJANZ, malignancies were observed in clinical studies and the post-marketing setting including but not limited to: lymphomas, lung cancer, breast cancer, colorectal cancer, gastric cancer, melanoma, prostate cancer, pancreatic cancer and renal cell carcinoma.

Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy. Recommendations for non-melanoma skin cancer are presented below.

Rheumatoid Arthritis

In the 5 controlled clinical studies, 5 malignancies (excluding non-melanoma skin cancers (NMSC)) were diagnosed in patients receiving XELJANZ 5 mg BID, and 8 malignancies (excluding NMSC) were diagnosed in patients receiving XELJANZ 10 mg BID, compared to 0 malignancies (excluding NMSC) in patients in the placebo/placebo plus DMARD group during the first 12 months. Lymphomas and solid cancers have also been observed in the long-term extension study in patients treated with XELJANZ (see **ADVERSE REACTIONS**). Patients with RA particularly those with highly active disease, may be at a higher risk (several fold) than the general population for the development of lymphoma.

In Phase 2B, controlled dose-ranging trials in de-novo renal transplant patients, all of whom received induction therapy with basiliximab, high dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine.

Psoriatic Arthritis

In the 2 controlled PsA clinical trials, there were 3 malignancies (excluding NMSC) in 474 patients receiving XELJANZ plus csDMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus csDMARD group (3 months exposure) and 0 malignancies in 106

patients in the adalimumab plus csDMARD group (12 months exposure). Malignancies have also been observed in the long-term extension study in PsA patients treated with XELJANZ.

Ulcerative Colitis
In the 4 controlled clinical studies for ulcerative colitis (up to 52-week treatment), no malignancies (excluding NMSC) were reported with XELJANZ. In the long-term extension open-label study, malignancies (excluding NMSC) have been observed in patients treated with XELJANZ 10 mg BID, including solid cancers and lymphoma.

Non-Melanoma Skin Cancer: Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. NMSC is a dose related adverse reaction, with a greater risk in patients treated with 10 mg BID of XELJANZ than in patients treated with 5 mg BID. Periodic skin examination is recommended.

In the UC 52-week maintenance study, NMSC was reported in 3 patients (1.5%) treated with 10 mg BID, as compared with no reported events in patients treated with 5 mg BID and 1 patient (0.5%) treated with placebo. In the long-term open label extension study, NMSC was reported in 6 patients in the 10 mg BID group and 2 patients in the 5 mg BID group.

Monitoring and Laboratory Tests
Lipid tests should be performed at baseline, approximately 4-8 weeks after initiation with XELJANZ/XELJANZ XR and every 6 months thereafter.

Liver enzymes tests are recommended. If DILI is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded.

Assessment of renal function is recommended prior to initiation of XELJANZ/XELJANZ XR (see **DOSAGE AND ADMINISTRATION**).

Lymphocyte, neutrophil and hemoglobin tests should be performed at baseline, approximately 4-8 weeks after initiation with XELJANZ/XELJANZ XR treatment, and every 3 months thereafter (see **DOSAGE AND ADMINISTRATION** for recommended dose adjustment based on these laboratory tests).

Vital signs: Patients should be monitored for pulse rate and blood pressure at baseline and periodically during treatment with XELJANZ/XELJANZ XR (see **WARNINGS AND PRECAUTIONS – Cardiovascular, ADVERSE REACTIONS,** and **DRUG INTERACTIONS**).

Musculoskeletal
Treatment with XELJANZ was associated with increases in creatine kinase (CK). Maximum effects were generally observed within 6 months. Rhabdomyolysis was reported in one patient treated with XELJANZ. Creatine kinase levels should be checked in patients with symptoms of muscle weakness and/or muscle pain to evaluate for evidence of rhabdomyolysis. Increases in CK were reported more frequently in patients treated with XELJANZ 10 mg as compared to those treated with 5 mg BID (see **ADVERSE REACTIONS**).

Renal

XELJANZ XR is not recommended in patients with moderate (CLcr ≥30 and <60 mL/min), or severe renal insufficiency (CLcr ≥15 and <30 mL/min), including patients with end-stage renal disease (ESRD) but not limited to those undergoing hemodialysis.

Dosage adjustment of XELJANZ is recommended in patients with moderate and severe renal impairment (see **WARNINGS AND PRECAUTIONS – Special Populations, DOSAGE AND ADMINISTRATION,** and **ACTION AND CLINICAL PHARMACOLOGY**). In clinical trials, XELJANZ was not evaluated in patients with baseline creatinine clearance values (estimated by the Cockcroft-Gault equation) less than 40 mL/min.

Respiratory

Interstitial Lung Disease: Events of interstitial lung disease (ILD) have been reported in RA clinical trials with XELJANZ, although the role of JAK inhibition in these events is not known. All patients who developed ILD were taking concomitant methotrexate, corticosteroids and/or sulfasalazine, which have been associated with ILD. Asian patients had an increased risk of ILD (see **WARNINGS AND PRECAUTIONS – Special Populations**).

XELJANZ/XELJANZ XR should be used with caution in patients with a risk or history of ILD.

Special Populations

Pregnant Women: XELJANZ/XELJANZ XR is contraindicated during pregnancy (see **CONTRAINDICATIONS**). There are no adequate and well-controlled studies on the use of XELJANZ/XELJANZ XR in pregnant women. XELJANZ has been shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility, parturition, and peri/postnatal development (see **TOXICOLOGY**).

Women of reproductive potential should be advised to use effective contraception during XELJANZ/XELJANZ XR treatment and for 4 to 6 weeks after the last dose.

Nursing Women: XELJANZ was secreted in milk of lactating rats. It is not known whether XELJANZ/XELJANZ XR is excreted in human milk. XELJANZ/XELJANZ XR is contraindicated in women who breastfeed (see **CONTRAINDICATIONS** and **TOXICOLOGY**).

Pediatrics (<18 years of age): The safety and effectiveness of XELJANZ/XELJANZ XR in pediatric patients have not been established. Therefore, XELJANZ/XELJANZ XR should not be used in this patient population (see **ACTION AND CLINICAL PHARMACOLOGY**).

Geriatrics (>65 years of age): The frequency of serious infection among XELJANZ treated subjects 65 years of age and older was higher than among those under the age of 65. Caution should be used when treating the elderly with XELJANZ/XELJANZ XR (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Asian Patients: Asian patients have an increased risk of herpes zoster and opportunistic infections. Asian patients with RA also have an increased risk of interstitial lung disease. An increased incidence of some adverse events such as elevated transaminases (ALT, AST) and decreased white

blood cells (WBCs) were also observed. Therefore, XELJANZ/XELJANZ XR should be used with caution in Asian patients (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Rheumatoid Arthritis

During controlled clinical trials, 8.0% (11.0 events/100 patient-years) of patients in the 5 mg BID in the XELJANZ group were hospitalized due to serious adverse reactions compared to 7.8% (9.1 events/100 patient-years) and 3.8% (13.0 events/100 patient-years) of patients in the adalimumab and placebo group, respectively.

The most common serious adverse reactions (SAEs) were osteoarthritis and serious infections, including pneumonia, cellulitis, herpes zoster, and urinary tract infection. During the first 3 months, serious infections (those requiring parenteral antibiotics or hospitalization) were reported in 0.7% (2.8 events/100 patient-years) and 0.2% (0.6 events/100 patient-years) of patients treated with XELJANZ or placebo, respectively. From 0-12 months, serious infections were reported in 2.4% (3.2 events/100 patient-years) of XELJANZ treated patients (see **WARNINGS AND PRECAUTIONS**).

Deaths occurred in 0.4% (0.6 events/100 patient-years) of patients in the 5 mg BID XELJANZ group, compared to 0.5% (0.6 events/100 patient-years) and 0.2% (0.5 events/100 patient-years) of patients in the adalimumab and placebo groups, respectively.

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials (occurring in ≥2% of patients treated with XELJANZ monotherapy or in combination with DMARDs) were upper respiratory tract infections, headache, nasopharyngitis, and diarrhea. Additionally, bronchitis, urinary tract infection, herpes zoster, rheumatoid arthritis, back pain and hypertension were also reported in the 5 mg BID XELJANZ group in the long-term extension trial.

The proportion of patients who discontinued treatment due to any adverse reactions during the first 3 months in double-blind placebo-controlled studies was 7.8% for patients taking 5 mg BID of XELJANZ and 3.7% for placebo-treated patients. In the long-term extension trial, the proportion of patients who discontinued treatment due to any adverse reaction was 24.8% (6.78 events/100 patient-years) for all patients, 27.9% (6.67 events/100 patient-years) for patients taking 5 mg BID of XELJANZ, and 23.8% (6.83 events/100 patient-years) for patients taking 10 mg BID of tofacitinib. The most common adverse reactions that resulted in discontinuation of XELJANZ were infections. Pneumonia was the most common adverse reactions leading to discontinuation of therapy, followed by blood creatinine increased and herpes zoster.

Following completion of the Phase 2/3, open-label, uncontrolled, long-term extension follow-up trial (up to 114 months) from the Phase 2 studies and Phase 3 clinical program, there were 4040 subjects with 16113 patient-years of exposure to tofacitinib. The design of the long-term safety studies allowed for modification of XELJANZ doses according to clinical judgment. This limits the interpretation of the long-term safety data with respect to dose. Tofacitinib 10 mg BID

is not recommended in RA patients. Overall, the safety profile of XELJANZ 5 mg BID in the long-term extension study was comparable to what was seen in the controlled clinical trials.

Asian Patients: Asian patients had higher rates of herpes zoster, opportunistic infections, elevated transaminases (ALT, AST) and decreased WBCs. Asian patients with RA also have an increased risk of interstitial lung disease. Therefore, XELJANZ/XELJANZ XR should be used with caution in Asian patients.

Psoriatic Arthritis
The safety data includes 2 double-blind, controlled, multicenter studies: study PsA-I (A3921091) with a 12-month duration and study PsA-II (A3921125) with a 6-month duration; both included a 3-month placebo-controlled period. All patients in the clinical studies were required to receive treatment with a stable dose of a csDMARD. An additional long-term, open-label clinical study was conducted and included patients with PsA who originally participated in either of the 2 double-blind, controlled clinical studies.

A total of 783 patients were treated with any dose of XELJANZ in PsA clinical studies resulting in 1238 patient-years of exposure. Of these, 635 patients were exposed to XELJANZ for at least one year.

The most common serious adverse reactions were serious infections. The most commonly reported adverse reactions (≥2%) in patients treated with XELJANZ 5 mg BID during the first 3 months in placebo-controlled clinical studies were bronchitis, diarrhea, dyspepsia, headache, nasopharyingitis, nausea.

The proportion of patients who discontinued treatment due to any adverse reactions during the first 3-months of the double-blind placebo-controlled studies was 3.2% for XELJANZ-treated patients and 2.5% for placebo-treated patients.

Overall, the safety profile observed in patients with active PsA treated with XELJANZ was consistent with the safety profile observed in patients with RA treated with XELJANZ.

Ulcerative Colitis
Four randomized, double-blind, placebo-controlled studies and one open-label study were conducted in patients with moderately to severely active UC: two similar 8-week pivotal Phase 3 induction studies (OCTAVE Induction 1 and 2), one 52-week pivotal Phase 3 maintenance study (OCTAVE Sustain), and one dose-ranging Phase 2 induction study (A3921063). A long-term open-label uncontrolled extensions study was also conducted (see **CLINICAL TRIALS**). In the 52-week OCTAVE Sustain study, 99 patients were treated with 5 mg BID and 113 patients with 10 mg BID for 52 weeks.

In the induction studies, the most common categories of serious adverse events were gastrointestinal disorders and infections. The most common serious adverse events (excluding events reported as ulcerative colitis) were abdominal pain, anal abscess, and drug hypersensitivity. The most common adverse events (≥5%) were headache and nasopharyngitis.

In the maintenance study, the most common categories of serious adverse events were gastrointestinal disorders, infections, injuries, and nervous system disorders. All serious adverse events were single reports (excluding events reported as ulcerative colitis). The most common adverse events (≥5%) (excluding events reported as ulcerative colitis) in patients treated with 5 mg BID were nasopharyngitis, arthralgia, headache, and upper respiratory tract infection. In patients treated with 10 mg BID, the most common adverse events were nasopharyngitis, arthralgia, blood creatine phosphokinase increased, upper respiratory tract infection, rash, hypercholesterolemia, and herpes zoster.

In induction studies, adverse events were reported in 515 subjects (54.9%) treated with 10 mg BID and 155 subjects (55.0%) treated with placebo. In the maintenance study, adverse events were reported in 143 subjects (72.2%) treated with 5 mg BID, 156 subjects (79.6%) treated with 10 mg BID, and 149 subjects (75.3%) treated with placebo.

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.

Four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily.

Overall, the safety profile observed in UC patients treated with XELJANZ was consistent with the safety profile of XELJANZ across indications. Dose-dependent risks seen in patients treated with XELJANZ 10 mg BID in comparison with 5 mg BID include the following: herpes zoster infections, serious infections, and NMSC.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Rheumatoid Arthritis

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

Table 1: Summary of Adverse Events Reported by ≥1% of RA Patients Treated with XELJANZ (All Causalities) - All Phase 3 Studies (up to 3 months)

Body System/Adverse Event	XELJANZ 5mg BID (N=1216)	Placebo (N=681)	Adalimumab 40 mg SC q2w (N=204)
Infections and infestations			
Upper respiratory tract infection	53 (4.4)	23 (3.4)	7 (3.4)
Nasopharyngitis	48 (3.9)	19 (2.8)	7 (3.4)
Urinary tract infection	25 (2.1)	12 (1.8)	7 (3.4)
Bronchitis	14 (1.2)	10 (1.5)	4 (2.0)

Body System/Adverse Event	XELJANZ 5mg BID (N=1216)	Placebo (N=681)	Adalimumab 40 mg SC q2w (N=204)
Blood and lymphatic system disorders			
Anemia	15 (1.2)	8 (1.2)	0
Metabolism and nutrition disorders			
Hypercholesterolaemia	12 (1.0)	3 (0.4)	1 (0.5)
Nervous system disorders			
Headache	54 (4.4)	15 (2.2)	5 (2.5)
Dizziness	13 (1.1)	8 (1.2)	3 (1.5)
Vascular disorders			
Hypertension	20 (1.6)	7 (1.0)	0
Gastrointestinal disorders			
Diarrhoea	45 (3.7)	16 (2.3)	2 (1.0)
Nausea	32 (2.6)	18 (2.6)	3 (1.5)
Dyspepsia	19 (1.6)	11 (1.6)	3 (1.5)
Abdominal pain upper	23 (1.9)	5 (0.7)	3 (1.5)
Vomiting	21 (1.7)	10 (1.5)	0
Constipation	16 (1.3)	6 (0.9)	2 (1.0)
Gastritis	12 (1.0)	7 (1.0)	0
Gastroenteritis	12 (1.0)	5 (0.7)	0
Hepatobiliary Disorders			
Alanine aminotransferase increased	14 (1.2)	7 (1.0)	1 (0.5)
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis	17 (1.4)	17 (2.5)	1 (0.5)
Back pain	18 (1.5)	5 (0.7)	1 (0.5)
Arthralgia	13 (1.1)	16 (2.3)	4 (2.0)
General disorders and administration site conditions			
Oedema peripheral	17 (1.4)	16 (2.3)	3 (1.5)
Pyrexia	13 (1.1)	5 (0.7)	1 (0.5)

Psoriatic Arthritis

The incidence rates and types of adverse drug reactions reported in the two controlled Phase 3 PsA clinical studies were generally similar to those reported in RA clinical studies.

Ulcerative Colitis

Table 2 below lists adverse drug reactions reported by ≥1% of patients treated with XELJANZ – UC Phase 2 and Phase 3 Induction Studies

Table 2: Summary of Adverse Drug Reactions (adverse events for which there is evidence of causality) Reported by ≥1% of Patients Treated with XELJANZ – UC Phase 2 and Phase 3 Induction Studies (up to 8 weeks)

Body System[±]/Adverse Drug Reaction	XELJANZ 10 mg BID (N=938)	Placebo (N=282)
Subjects with one or more ADR (%)	494 (52.7)	130 (46.1)
Blood and lymphatic system disorders	26 (2.8)	10 (3.5)
Anemia	22 (2.3)	9 (3.2)
Gastrointestinal disorders	82 (8.7)	26 (9.2)
Nausea	28 (3.0)	11 (3.9)

Body System±/Adverse Drug Reaction	XELJANZ 10 mg BID (N=938)	Placebo (N=282)
Abdominal pain	25 (2.7)	11 (3.9)
Vomiting	9 (1.0)	3 (1.1)
Dyspepsia	12 (1.3)	1(0.4)
General disorders and administration site conditions	48 (5.1)	13 (4.6)
Fatigue	17 (1.8)	5 (1.8)
Pyrexia	24 (2.6)	4 (1.4)
Infections and infestations	111 (11.8)	24 (8.5)
Nasopharyngitis	56 (6.0)	14 (5.0)
Influenza	9 (1.0)	3 (1.1)
Urinary tract infection	11 (1.2)	1 (0.4)
Pharyngitis	10 (1.1)	1 (0.4)
Investigations	65 (6.9)	4 (1.4)
Blood creatine phosphokinase increased	25 (2.7)	3 (1.1)
Elevated cholesterol levels*	31 (3.3)	0
Musculoskeletal and connective tissue disorders	33 (3.5)	12 (4.3)
Arthralgia	27 (2.9)	12 (4.3)
Nervous system disorders	77 (8.2)	20 (7.1)
Headache	73 (7.8)	19 (6.7)
Respiratory	14 (1.5)	8 (2.8)
Cough	13 (1.4)	7 (2.5)
Skin and Subcutaneous Tissue Disorders	18 (1.9)	9 (3.2)
Rash	12 (1.3)	2 (0.7)
Vascular disorders	9 (1.0)	1 (0.4)
Hypertension	9 (1.0)	1 (0.4)

* includes: hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased.
± the total number of subjects with adverse reactions and the total number of subjects with adverse reactions for each body system include all adverse drug reactions (those reported by ≥1% of subjects treated with XELJANZ and those reported by <1% of subjects treated with XELJANZ); the total also includes some subjects who reported more than one adverse drug reaction (which inflates the percentage).

Table 3: Summary of Adverse Drug Reactions (adverse events for which there is evidence of causality) Reported by ≥1% of Patients Treated with XELJANZ – UC Phase 3 Maintenance Study (up to 12 months)

Body System±/Adverse Drug Reaction	XELJANZ 5mg BID (N=198)	XELJANZ 10mg BID (N=196)	Placebo (N=198)
Subjects with one or more ADR (%)	166 (83.8)	207 (100)	153 (77.3)
Blood and lymphatic system disorders	9 (4.5)	5 (2.6)	3 (1.5)
Anemia	8(4.0)	4 (2.0)	3 (1.5)
Gastrointestinal disorders	16 (8.1)	32 (16.3)	26 (13.1)
Diarrhea	3 (1.5)	9 (4.6)	5 (2.5)
Nausea	1 (0.5)	8 (4.1)	5 (2.5)
Abdominal pain	5 (2.5)	7 (3.6)	11 (5.6)
Vomiting	3 (1.5)	6 (3.1)	2 (1.0)
Dyspepsia	4 (2.0)	1 (0.5)	2 (1.0)
General disorders and administration	12 (6.1)	11 (5.6)	17 (8.6)

Body System±/Adverse Drug Reaction	XELJANZ 5mg BID (N=198)	XELJANZ 10mg BID (N=196)	Placebo (N=198)
site conditions			
Fatigue	8 (4.0)	4 (2.0)	11 (5.6)
Pyrexia	3 (1.5)	6 (3.1)	5 (2.5)
Infections and infestations	51 (25.8)	65 (33.2)	37 (18.7)
Nasopharyngitis	19 (9.6)	27 (13. 8)	11 (5.6)
Herpes zoster	3 (1.5)	10 (5.1)	1 (0.5)
Influenza	4 (2.0)	7 (3.6)	7 (3.5)
Urinary tract infection	5 (2.5)	6 (3.1)	4 (2.0)
Bronchitis	5 (2.5)	6 (3.1)	3 (1.5)
Sinusitis	6 (3.0)	2 (1.0)	2 (1.0)
Pharyngitis	6 (3.0)	1 (0.5)	3 (1.5)
Gastroenteritis viral	0	3 (1.5)	2 (1.0)
Viral infection	2 (1.0)	1 (0.5)	1 (0.5)
Injury, poisoning and procedural complications	2 (1.0)	2 (1.0)	0
Ligament sprain	1 (0.5)	2 (1.0)	0
Investigations	19 (9.6)	38 (19.4)	7 (3.5)
Elevated cholesterol levels*	9 (4.5)	18 (9.2)	3 (1.5)
Blood creatine phosphokinase increased	6 (3.0)	13 (6.6)	4 (2.0)
Weight increased	3 (1.5)	4 (2.0)	0
Gamma glutamyltransferase increased,	1 (0.5)	3 (1.5)	0
Musculoskeletal and connective tissue disorders	19 (9.6)	19 (9.7)	25 (12.6)
Arthralgia	17 (8.6)	17 (8.7)	19 (9.6)
Musculoskeletal pain	1 (0.5)	2 (1.0)	5 (2.5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	2 (1.0)	1 (0.5)
Non-melanoma skin cancers	0	2 (1.0)	1 (0.5)
Nervous system disorders	18 (9.1)	7 (3.6)	12 (6.1)
Headache	17 (8.6)	6 (3.1)	12 (6.1)
Psychiatric	3 (1.5)	1 (0.5)	1 (0.5)
Insomnia	3 (1.5)	1 (0.5)	1 (0.5)
Respiratory	6 (3.0)	8 (4.1)	6 (3.0)
Cough	6 (3.0)	5 (2.6)	5 (2.5)
Dyspnea	0	2 (1.0)	1 (0.5)
Skin and Subcutaneous Tissue Disorders	7 (3.5)	12 (6.1)	17 (8.6)
Rash	6 (3.0)	11 (5.6)	8 (4.0)
Vascular disorders	4 (2.0)	4 (2.0)	1 (0.5)
Hypertension	4 (2.0)	4 (2.0)	1 (0.5)

***** includes: hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased.

± The total number of subjects with adverse reactions and the total number of subjects with adverse reactions for each body system include all adverse drug reactions (those reported by ≥1% of subjects treated with XELJANZ and those reported by <1% of subjects treated with XELJANZ); the total also includes some subjects who reported more than one adverse drug reaction (which inflates the percentage).

Overall Infections

Rheumatoid Arthritis

In the five controlled trials, during 0 to 3 months exposure, the overall frequency of infections was 20% in the 5 mg BID XELJANZ group, and 18% in the placebo group.

In the long-term extension trial, overall frequency of infections was 67.7% (39.63 events/100 patient-years) in all XELJANZ group; 65.5% of patients (33.22 events/100 patient-years) and 68.4% of patients (42.24 events/100 patient-years) in the 5 mg and 10 BID of tofacitinib, respectively.

The most commonly reported infections were upper respiratory tract infections, nasopharyngitis, bronchitis, herpes zoster, and urinary tract infections.

Psoriatic Arthritis
The incidence rates and types of overall infections in the two controlled Phase 3 PsA clinical studies were generally similar to those reported in RA clinical studies.

Ulcerative Colitis
In the randomised 8-week Phase 2/3 induction studies, the proportions of patients with infections were 21.1% (198 patients) in the XELJANZ 10 mg BID group compared to 15.2% (43 patients) in the placebo group. In the randomised 52-week Phase 3 maintenance study, the proportion of patients with infections were 35.9% (71 patients) in the 5 mg BID and 39.8% (78 patients) in the 10 mg BID XELJANZ groups, compared to 24.2% (48 patients) in the placebo group.

In the maintenance study, results suggested that the risk of opportunistic infection was possibly dose related: XELJANZ 10 mg BID (2.0%), XELJANZ 5 mg BID (1.0%), and placebo (0.5%). All opportunistic infections were herpes zoster infections. Herpes zoster was reported more frequently with XELJANZ 10 mg BID (5.1%), as compared to XELJANZ 5 mg BID (1.5%), or placebo (0.5%), indicating that the risk of herpes zoster is dose related.

In the entire treatment experience with XELJANZ, the most commonly reported infection was nasopharyngitis, occurring in 18.2% of patients (211 patients).

Serious Infections
Rheumatoid Arthritis
In the five controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.6 events/100 patient-years) who received placebo and 8 patients (2.8 events/100 patient-years) who received 5 mg BID of XELJANZ.

During the 0 to 12 months exposure, the overall frequencies of serious infections were 2.4% (3.2 events/100 patient-years) for the 5 mg BID XELJANZ group.

In the long-term extension trial, the most common serious infections reported with XELJANZ included pneumonia, cellulitis, appendicitis, diverticulitis, gastroenteritis, urinary tract infection, and herpes zoster (see **WARNINGS AND PRECAUTIONS**).

Psoriatic Arthritis
The incidence rates and types of serious infections in the two controlled Phase 3 PsA clinical studies were generally similar to those reported in RA clinical studies.

Ulcerative Colitis
The incidence rates and types of serious infections in the UC clinical trials were generally similar to those reported in RA clinical trials with XELJANZ.

Patients treated with XELJANZ 10 mg BID had a higher rate of serious infections compared to those treated with 5 mg twice daily.

Tuberculosis
Cases of tuberculosis have been reported with treatment with XELJANZ.

Rheumatoid Arthritis
In the five controlled trials, during 0 to 3 months exposure, no cases of tuberculosis were reported in patients who received placebo or 5 mg BID of XELJANZ.

During the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg BID of XELJANZ.

In the long-term extension trial, adjudicated tuberculosis events were reported in 0.6% patients (0.15 events/100 patient-years) who received XELJANZ; 0.4% of patients (0.10 events/100 patient-years) and 0.6% of patients (0.17 events/100 patient-years) in the 5 mg and 10 mg BID of tofacitinib, respectively.

Cases of disseminated tuberculosis were also reported. The median XELJANZ exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days) (see **WARNINGS AND PRECAUTIONS**).

Psoriatic Arthritis
The incidence rates of tuberculosis in the two controlled Phase 3 PsA clinical studies were generally similar to those reported in RA clinical studies.

Opportunistic Infections (excluding tuberculosis)
Rheumatoid Arthritis
In the five controlled trials, during 0 to 3 months exposure, opportunistic infections were reported in 0 patients who received placebo and 2 (0.2%) patients (0.7 events/100 patient-years) who received 5 mg BID of XELJANZ.

During the 0 to 12 months exposure, opportunistic infections were reported in 3 (0.3%) patients (0.3 events/100 patient-years) who received 5 mg BID of XELJANZ.

The median XELJANZ exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days).

The similar frequency of opportunistic infections was observed in the long-term extension trial with XELJANZ treatment up to 114 months.

Psoriatic Arthritis

The incidence rates and types of opportunistic infections in the two controlled Phase 3 PsA clinical studies were generally similar to those reported in RA clinical studies.

Ulcerative Colitis
In the maintenance study, herpes zoster was reported more frequently with XELJANZ 10 mg BID (5.1%), as compared to XELJANZ 5 mg BID (1.5%), or placebo (0.5%), indicating that the risk of herpes zoster is dose related.

Also, opportunistic herpes zoster infections (including serious cases, such as, disseminated, meningoencephalitis, ophthalmologic) were reported in patients treated with XELJANZ 10 mg twice daily.

Malignancy (excluding non-melanoma skin cancer)
Rheumatoid Arthritis
In the five controlled trials, during the 0 to 3 months exposure, malignancies (excluding non-melanoma skin cancer) were reported in 0 patients who received placebo and 2 (0.2%) patients (0.7 events/100 patient-years) who received 5 mg BID of XELJANZ.

During the 0 to 12 months exposure, malignancies (excluding non-melanoma skin cancer) were reported in 5 (0.4%) patients (0.6 events/100 patient-years) who received 5 mg BID of XELJANZ.

In the long-term extension trial, overall frequency of malignancies (excluding non-melanoma skin cancer) was 3.1% (0.83 events/100 patient-years) in all XELJANZ-treated patients; 3.4% of patients (0.8 events/100 patient-years) and 3% of patients (0.84 events/100 patient-years) in the 5 mg and 10 mg BID of tofacitinib, respectively.

The most common types of malignancy (excluding non-melanoma skin cancer), including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma and malignant melanoma (see **WARNINGS AND PRECAUTIONS**).

Psoriatic Arthritis
The incidence rates of malignancies (excluding NMSC) in the two controlled Phase 3 PsA clinical studies were generally similar to those reported in RA clinical studies.

Ulcerative Colitis
In the controlled clinical studies (up to 52-week treatment), no malignancies (excluding NMSC) were reported with XELJANZ.

In the long-term extension open-label study, malignancies (excluding NMSC) have been observed in patients treated with XELJANZ 10 mg BID, including solid cancers and lymphoma.

Non-Melanoma Skin Cancer
NMSC is a dose related adverse reaction, with a greater risk in patients treated with 10 mg BID of XELJANZ than in patients treated with 5 mg BID.

Rheumatoid Arthritis

In the five controlled trials, during the 0 to 3 months exposure, NMSC was reported in 1 (0.2%) patient (0.6 events/100 patient-years) who received placebo and 2 (0.2%) patients (0.7 events/100 patient-years) who received 5 mg BID of XELJANZ.

During the 0 to 12 months exposure, NMSC was reported in 3 (0.3%) patients (0.3 events/100 patient-years) who received 5 mg BID of XELJANZ.

In the long-term extension trial, overall frequency of NMSC was 2.6% (0.71 events/100 patient-years) in all XELJANZ-treated patients; 2.5% of patients (0.6 events/100 patient-years) and 2.6% of patients (0.75 events/100 patient-years) in the 5 mg and 10 mg BID of tofacitinib, respectively.

Psoriatic Arthritis
The incidence rates of NMSC in the two controlled Phase 3 PsA clinical studies were generally similar to those reported in RA clinical studies.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Rheumatoid Arthritis
Blood and Lymphatic System Disorders: neutropenia, leukopenia, lymphopenia
Cardiovascular: congestive heart failure, myocardial infarction
Gastrointestinal Disorders: abdominal pain
General Disorders and Administration Site Conditions: influenza
Hepatobiliary Disorders: hepatic steatosis
Infections and Infestations: sepsis, pneumonia bacterial, pneumonia pneumococcal, pyelonephritis, cellulitis, gastroenteritis viral, viral infection, herpes simplex, herpes zoster. tuberculosis of central nervous system, encephalitis, necrotising fasciitis, meningitis cryptococcal, disseminated tuberculosis, urosepsis, pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, tuberculosis, arthritis bacterial, atypical mycobacterial infection, mycobacterium avium complex infection, cytomegalovirus infection, bacteraemia, diverticulitis
Injury, Poisoning and Procedural Complications: muscle strain, fall
Investigations: transaminases increased, blood creatinine increased, gamma glutamyltransferase increased, liver function test abnormal, weight increased, blood creatine phosphokinase increased, hepatic enzyme increased, low density lipoprotein increased, blood cholesterol increased
Metabolism and Nutrition Disorders: dehydration, dyslipidemia, hyperlipidemia
Musculoskeletal and Connective Tissue Disorders: tendonitis, joint swelling, musculoskeletal pain, ligament sprain
Neoplasm Benign, Malignant and Unspecified (Including Cysts and Polyps): non-melanoma skin cancers
Nervous System Disorders: paraesthesia
Psychiatric Disorders: insomnia
Respiratory, Thoracic and Mediastinal Disorders: sinus congestion, cough, dyspnoea
Skin and Subcutaneous Tissue Disorders: erythema, pruritus

Psoriatic Arthritis
The incidence rates of less common clinical trial adverse drug reactions (<1%) in the two controlled Phase 3 PsA clinical studies were generally similar to those reported in RA clinical studies.

Ulcerative Colitis
Blood and Lymphatic System Disorders: neutropenia, lymphopenia, leukopenia
Gastrointestinal Disorders: gastritis
General Disorders and Administration Site Conditions: oedema peripheral
Hepatobiliary Disorders: hepatic steatosis
Infections and Infestations: pneumonia, pyelonephritis, cellulitis, herpes simplex, tuberculosis, arthritis bacterial, cytomegalovirus infection, diverticulitis
Injury, Poisoning and Procedural Complications: muscle strain
Investigations: hepatic enzyme increased**,** transaminases increased, blood creatinine increased, liver function test abnormal, low density lipoprotein increased
Metabolism and Nutrition Disorders: dehydration
Musculoskeletal and Connective Tissue Disorders: tendonitis, joint swelling
Neoplasm Benign, Malignant and Unspecified (Including Cysts and Polyps): non-melanoma skin cancers, solid cancers, lymphomas
Nervous System Disorders: paraesthesia
Respiratory, Thoracic and Mediastinal Disorders: sinus congestion
Skin and Subcutaneous Tissue Disorders: erythema, pruritus

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory Tests – Rheumatoid Arthritis and Ulcerative Colitis
Creatine Kinase
Treatment with XELJANZ was associated with increases in creatine kinase (CK). Maximum effects were generally observed within 6 months. Rhabdomyolysis was reported in one patient treated with XELJANZ.

CK levels should be checked in patients with symptoms of muscle weakness and/or muscle pain to evaluate for evidence of rhabdomyolysis (see **WARNINGS AND PRECAUTIONS**).

ECG Findings
In placebo-controlled Phase 2 clinical trials, steady-state treatment with 5-10 mg BID XELJANZ was associated with statistically significant 4-7 bpm decreases in heart rate and 4-10 ms increases in the PR interval compared with placebo (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

Lipids
Treatment with XELJANZ was associated with dose related increases in lipid parameters.

Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) generally reached maximal effects at 6 weeks following initiation of XELJANZ in the controlled RA double-blind clinical trials. Changes in lipid parameters from baseline through the end of the study (6-12 months) in the controlled clinical studies in RA are summarized below:

- Mean LDL cholesterol increased by 14% in the XELJANZ 5 mg BID arm.
- Mean HDL cholesterol increased by 16% in the XELJANZ 5 mg BID arm.
- Mean LDL/HDL ratios were essentially unchanged in XELJANZ-treated patients.

In the five controlled RA clinical trials, 4.4% of patients treated with 5 mg BID, initiated lipid-lowering medication while on study.

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

Liver Enzyme Tests

Confirmed increases in liver enzymes >3x upper limit of normal (ULN) were uncommonly observed. In those 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 RA Phase 3 monotherapy study (0-3 months), ALT elevations >3x ULN were observed in 1.65% and 0.41% of patients receiving placebo and 5 mg BID, respectively. In this study, AST elevations >3x ULN were observed in 1.65%, and 0.41% of patients receiving placebo and 5 mg BID, respectively.

In the controlled portion of the RA Phase 3 studies on background DMARDs (0-3 months), ALT elevations >3x ULN were observed in 0.9% and 1.24% of patients receiving placebo and 5 mg BID, respectively. In these studies, AST elevations >3x ULN were observed in 0.72% and 0.52% of patients receiving placebo and 5 mg BID, respectively.

In the RA long-term extension trial, ALT and AST elevations greater than 3x ULN were observed in 2.2% and 1.1% of all XELJANZ-treated patients, respectively. Overall, total bilirubin elevations greater than 2x ULN were observed in 3 (0.1%) patients. Increases to ≥5x and ≥10x ULN were observed for both ALT (0.5% and 0.2% of patients, respectively) and AST (0.3% and 0.1% of patients, respectively) in all patients treated with XELJANZ.

In RA patients taking 5 mg BID of XELJANZ, the ALT and AST elevations greater than 3x ULN were observed in 2.4% and 1.3% of patients, respectively. There was no subject who had the total bilirubin elevations greater than 2x ULN. Increases to ≥5 and ≥10x ULN were observed for both ALT (0.4% and 0.1% of patients, respectively) and AST (0.2% and 0% of patients, respectively).

In RA patients taking 10 mg twice daily of tofacitinib, the ALT and AST elevations greater than 3x ULN were observed in 2.1% and 1.1% of patients, respectively. The total bilirubin elevations greater than 2x ULN were observed in 3 (0.1%) patients. Increases to ≥5 and ≥10x ULN were observed for both ALT (0.5% and 0.2% of patients, respectively) and AST (0.3% and 0.1% of patients, respectively).

Two patients treated with 10 mg BID of tofacitinib in the RA long-term extension trial were assessed as probable DILI by the adjudication committee. One of the two patients had other possible causes of alcohol intake and methotrexate.

In the clinical studies in UC, changes in liver enzyme tests observed with XELJANZ 5 mg BID treatment were similar to the changes observed in clinical studies in RA.

In UC patients, XELJANZ treatment with 5 and 10 mg BID was also associated with an increased incidence of liver enzyme elevation compared to placebo, with a trend for higher incidence with the 10 mg BID as compared to the 5 mg BID dose.

One patient with XELJANZ 10 mg BID in the maintenance UC study experienced an increase in liver enzymes which decreased upon discontinuation of treatment. The case was adjudicated as possible DILI, while noting ultrasound findings of fatty liver.

Lymphocytes

In the five controlled RA clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm^3 occurred in 0.2% of patients for the 5 mg BID XELJANZ group during 12 months of exposure.

Confirmed lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections (see **WARNINGS AND PRECAUTIONS**).

In the RA long-term extension trial, cases of lymphopenia have been reported in 181 (4.0%) patients (1.11 events/100 patient-years) treated with XELJANZ; 4.5% of patients (1.07 events/100 patient-years) and 3.9% of patients (1.12 events/100 patient-years) in the 5 mg and 10 mg BID of tofacitinib, respectively. Confirmed decreased in absolute lymphocyte counts below 500 cells/mm^3 occurred in 1.3% of all XELJANZ-treated patients; 1.1% of patients for the 5 mg BID XELJANZ group, and 1.4% of patients for the 10 mg BID tofacitinib group.

In the 52-week maintenance study in UC, a single absolute lymphocyte count below 500 cells/mm^3 was reported in 2.6% (n=5) of patients treated with 10 mg BID, and was not reported in patients treated with 5 mg BID or placebo. No patients in any treatment group had confirmation of a lymphocyte count below 500 cells/mm^3 based on two sequential tests.

Neutrophils

In the controlled RA clinical studies, confirmed decreases in ANC below 1000/mm^3 occurred in 0.08% of patients in the 5 mg BID XELJANZ group during 12 months of exposure. There were no confirmed decreases in ANC below 500/mm^3 observed in any treatment group.

There was no clear relationship between neutropenia and the occurrence of serious infections.

In the long-term extension trial, cases of neutropenia have been reported in 86 (1.9%) patients (0.52 events/100 patient-years) treated with XELJANZ; 4.0% of patients (0.97 events/100 patient-years) and 1.2% of patients (0.35 events/100 patient-years) in the 5 mg and 10 mg BID of tofacitinib, respectively. Confirmed decreased in ANC below 1000 cells/mm^3 occurred in 0.2% in all XELJANZ-treated patients; 0.4% of patients for the 5 mg BID XELJANZ group, and 0.1% of patients for the 10 mg BID tofacitinib group.

In the clinical studies in UC, changes in neutrophils observed with XELJANZ treatment were similar to the changes observed in clinical studies in RA.

Serum Creatinine

In the controlled RA clinical trials, dose-related elevations in serum creatinine were observed with XELJANZ treatment. The mean increase in serum creatinine was <0.1 mg/dL in the 12-month pooled safety analysis; however, with increasing duration of exposure in the long-term extension trial, up to 6.9% of patients were discontinued from XELJANZ treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

In the UC studies, an increase of more than 50% in serum creatinine was reported in 1.6% of patients predominantly treated with XELJANZ 5 mg BID, and 3.4% of those predominantly treated with XELJANZ 10 mg BID.

Laboratory Tests – Psoriatic Arthritis

In the controlled clinical trials in PsA, changes in hematologic and clinical chemistry findings observed with XELJANZ treatment were similar to the changes observed in clinical trials in RA.

Post-Marketing Adverse Drug Reactions

Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: drug hypersensitivity reactions including angioedema and urticaria (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**)
Serious infections: viral reactivation (hepatitis B reactivation) (see **WARNINGS AND PRECAUTIONS**)

Vascular disorders: Thrombosis (deep vein thrombosis, pulmonary embolism, and arterial thrombosis) (see **WARNINGS AND PRECAUTIONS**)

DRUG INTERACTIONS

Overview

In vitro studies indicate that tofacitinib does not significantly inhibit 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 C_{max} of a 5 and 10 mg BID dose in patients treated with tofacitinib. In vitro studies also indicated a low risk of induction of CYP3A4 (2-fold mRNA at 6.25 μM), CYP2B6 (2-fold mRNA at 12.5 μM), and CYP1A2 (no enzyme changes) at clinically relevant concentrations (total C_{max} of 0.186 μM).

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. In vitro data indicate that the potential for tofacitinib to inhibit transporters such as P-glycoprotein, MDR1, organic anion transporter (OAT) P1B1/1B3, OCT2,

OAT1/3, cationic transporters or multidrug resistance-associated protein (MRP) at therapeutic concentrations is also low.

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

The 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 XELJANZ.

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 C_{max} of a 5 and 10 mg twice daily dose in RA, PsA and UC patients.

The oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalize CYP enzyme activity in patients. Therefore, coadministration with XELJANZ/XELJANZ XR is not expected to result in clinically relevant increases in the metabolism of CYP substrates.

Drug-Drug Interactions

Table 4: Summary of Drug-Drug Interactions

Drug	Reference	Effect	Clinical Comment
Methotrexate	CT	Coadministration with methotrexate (15-25 mg MTX once weekly) had no effect on the PK of tofacitinib and decreased methotrexate AUC (area under the curve) and C_{max} by 10% and 13% respectively.	No dose adjustment is required for either drug.

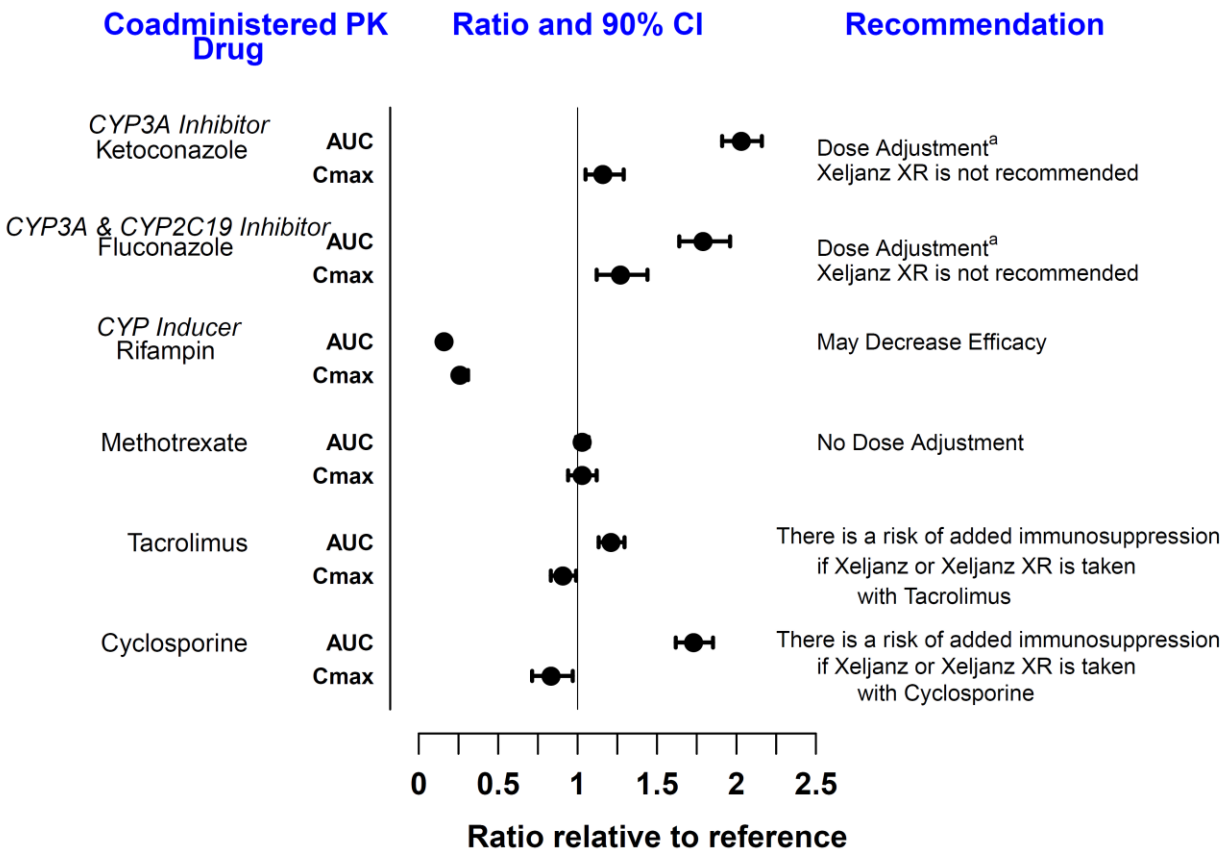
Drug	Reference	Effect	Clinical Comment
Ketoconazole	CT	Coadministration of ketoconazole, a strong CYP3A4 inhibitor, with a single dose of XELJANZ increased the AUC and C_{max} of tofacitinib by 103% and 16%, respectively	XELJANZ XR is not recommended in patients coadministered with strong inhibitors of CYP3A4. The recommended dose is half the daily dose indicated for patients not receiving strong CYP3A4 inhibitors concomitantly, i.e., in patients already taking: XELJANZ 10 mg twice daily, reduce the dose to XELJANZ 5 mg twice daily or XELJANZ 5 mg twice daily, reduce the dose to XELJANZ 5 mg once daily.
Fluconazole	CT	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	XELJANZ XR is not recommended in patients coadministered with medications that result in moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. The recommended dose is half the daily dose indicated for patients not receiving concomitant medications that result in moderate inhibition of CYP3A4 and potent inhibition of CYP2C19, i.e., in patients already taking: XELJANZ 10 mg twice daily, reduce the dose to XELJANZ 5 mg twice daily or XELJANZ 5 mg twice daily, reduce the dose to XELJANZ 5 mg once daily.
Tacrolimus and Cyclosporine	CT	Coadministration of tacrolimus, a mild inhibitor of CYP3A4, increased the AUC of tofacitinib by 21% and decreased the C_{max} of tofacitinib by 9%. Coadministration of cyclosporine, a moderate inhibitor of CYP3A4, increased the AUC of tofacitinib by 73% and decreased C_{max} of tofacitinib by 17%.	There is a risk of added immunosuppression when XELJANZ/XELJANZ XR is co-administered with potent immunosuppressive drugs (e.g: tacrolimus, cyclosporine, azathioprine). The combined use with these potent immunosuppressives has not been studied in patients and is not recommended.

Drug	Reference	Effect	Clinical Comment
Rifampin	CT	Coadministration of rifampin, a strong CYP3A4 inducer, decreased the AUC and C_{max} of tofacitinib by 84% and 74%, respectively	Coadministration of XELJANZ/XELJANZ XR with potent inducers of CYP3A4 may result in loss of or reduced clinical response /efficacy.
Midazolam	CT	Coadministration of XELJANZ with midazolam, a highly sensitive CYP3A4 substrate, had no effect on midazolam PK	No dosage adjustment is required for CYP3A4 substrates such as midazolam.
Oral contraceptives (Ethinyl Estradiol and Levonorgestrel)	CT	Coadministration of XELJANZ with oral contraceptives had no effect on the PK of either oral contraceptive in healthy females	No dose adjustment is required for either oral contraceptives (ethinyl estradiol and levonorgestrel).
Metformin	CT	Coadministration of XELJANZ with metformin, a substrate of Organic Cationic Transporter and Multidrug and Toxic Compound Extrusion, had no effect on the PK of metformin	No dosage adjustment is required for metformin.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

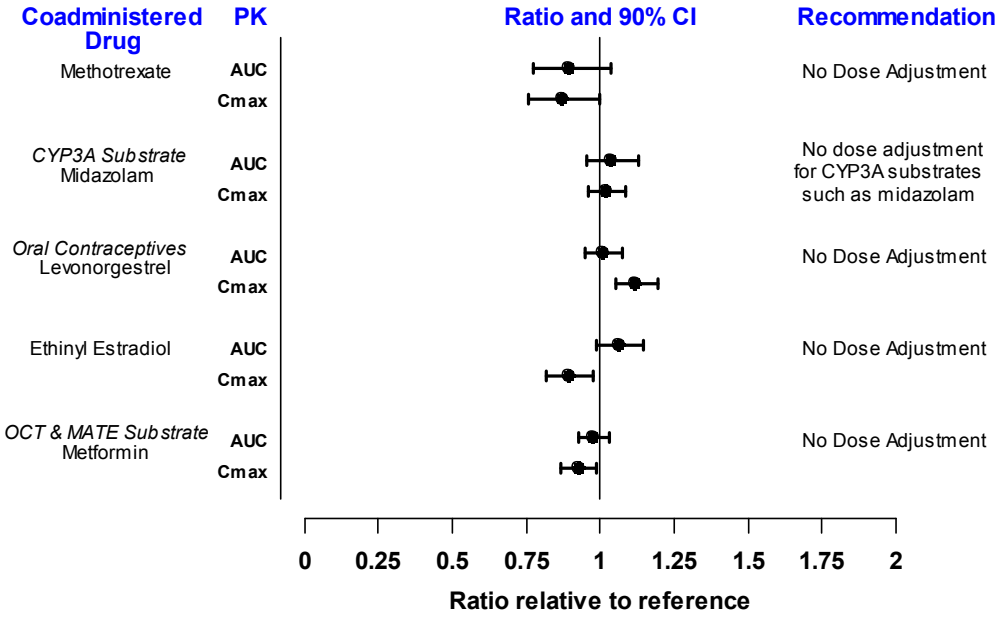
The impact of extrinsic factors on tofacitinib pharmacokinetics is summarized in Figure 1 and 2 with dosage adjustment recommendations.

Figure 1: Impact of Co-administered of drugs on Pharmacokinetics Tofacitinib



Note: Reference group is administration of tofacitinib alone; PK=Pharmacokinetics; CI=Confidence Interval
[a] In RA patients the recommended dose is XELJANZ 5 mg once daily. In UC patients receiving 10 mg twice daily, XELJANZ dosage should be reduced to 5 mg twice daily, and in UC patients receiving 5 mg twice daily, XELJANZ dosage should be reduced to 5 mg once daily.

Figure 2: Impact of Tofacitinib on Pharmacokinetics of Co-administered Drugs



Note: Reference group is administration of concomitant medication alone; OCT = Organic Cationic Transporter; MATE = Multidrug and Toxic Compound Extrusion; PK=Pharmacokinetics; CI=Confidence Interval

Drugs that Decrease Heart Rate and/or Prolong the PR Interval

XELJANZ resulted in a decrease in heart rate and an increase in the PR interval (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**). Caution should be observed if XELJANZ/XELJANZ XR is used concomitantly with other drugs that lower heart rate and/or prolong the PR interval, such as antiarrhythmics, beta blockers, alpha2 adrenoceptor agonists, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, and some HIV protease inhibitors.

Combination with other therapies

XELJANZ/XELJANZ XR has not been studied and is not indicated to be used in combination with biologics such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, IL-17 antagonists, IL-12/IL-23 antagonists, anti-CD20 monoclonal antibodies, anti-integrins, selective co-stimulation modulators, and potent immunosuppressants such as azathioprine, 6-mercaptopurine, cyclosporine, and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

The use of XELJANZ/XELJANZ XR in combination with phosphodiesterase 4 inhibitors has not been studied in XELJANZ clinical trials.

Drug-Food Interactions

Grapefruit juice affects CYP450 3A-mediated metabolism and concomitant administration with XELJANZ/XELJANZ XR should be avoided.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

Drug-Herb Interactions
St John's Wort is a CYP3A4 inducer and co-administration with XELJANZ/XELJANZ XR may result in loss of or reduced clinical response.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations
There is a risk of added immunosuppression when XELJANZ/XELJANZ XR is coadministered with potent immunosuppressive drugs (e.g. azathioprine, tacrolimus, cyclosporine). Combined use of XELJANZ/XELJANZ XR with potent immunosuppressants or biologic DMARDS (tumor necrosis factor (TNF) antagonists, interleukin 1 receptor (IL-1R) antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists and selective co-stimulation modulators) has not been studied in RA, PsA and UC patients and its use should be avoided.

Recommended Dose and Dosage Adjustment

Rheumatoid Arthritis XELJANZ/XELJANZ XR Posology
Adults: XELJANZ/XELJANZ XR is to be used in combination with methotrexate.

XELJANZ/XELJANZ XR, monotherapy may be considered in cases of intolerance to methotrexate.

The recommended dose of XELJANZ is 5 mg administered twice daily. The recommended dose of XELJANZ XR is 11 mg once daily

XELJANZ/XELJANZ XR is given orally with or without food.

Swallow XELJANZ XR tablets whole and intact. Do not crush, split, or chew.

Switching between XELJANZ Tablets and XELJANZ XR Tablets: Where appropriate, patients treated with XELJANZ 5 mg twice daily may be switched to XELJANZ XR 11 mg once daily the day following the last dose of XELJANZ 5 mg.

Where appropriate, patients treated with XELJANZ XR 11 mg once daily may be switched to XELJANZ 5 mg twice daily 24 hours following the last dose of XELJANZ XR 11 mg.

Patients treated with XELJANZ XR 11 mg once daily who require a dose reduction due to renal or hepatic impairment or drug interactions may be switched to XELJANZ 5 mg once daily,

24 hours following the last dose of XELJANZ XR 11 mg once daily (see **WARNINGS AND PRECAUTIONS** and **DRUG INTERACTIONS**).

Psoriatic Arthritis XELJANZ Posology
Adults: The recommended dose of XELJANZ is 5 mg administered twice daily in combination with MTX or another csDMARD.

Ulcerative Colitis XELJANZ Posology
Adults: The recommended dose is 10 mg given orally twice daily for induction for at least 8 weeks and 5 mg given twice daily for maintenance.

Depending on therapeutic response; 10 mg twice daily may also be used for maintenance in some patients. However, the lowest effective dose possible should be used for maintenance therapy to minimize adverse effects (see **WARNINGS AND PRECAUTIONS**).

XELJANZ induction therapy should be discontinued in patients who show no evidence of adequate therapeutic benefit by Week 16.

In patients who have responded to treatment with XELJANZ, corticosteroids may be cautiously reduced and/or discontinued in accordance with standard of care.

Dose Modification due to Serious Infections and Cytopenias (see Tables 5-7 below)

- It is recommended that XELJANZ/XELJANZ XR not be initiated in patients with an absolute neutrophil count (ANC) less than 1000/mm^3, hemoglobin (Hgb) levels <9 g/d, or with a lymphocyte count less than 500 cells/mm^3 (see **WARNINGS AND PRECAUTIONS**).
- Dose interruption is recommended for management of lymphopenia, neutropenia and anemia (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).
- Avoid use of XELJANZ/XELJANZ XR if a patient develops a serious infection until the infections is controlled.

Table 5: Dose Adjustments for Neutropenia

Low ANC	
Lab Value (cells/mm^3)	**Recommendation**
ANC >1000	Maintain dose
ANC 500-1000	For persistent decreases in this range, interrupt or reduce administration with XELJANZ/XELJANZ XR until ANC is >1000 cells/mm^3 • For patients receiving XELJANZ 5 mg twice daily, interrupt XELJANZ dosing. When ANC is >1000, resume XELJANZ 5 mg twice daily. RA patients: • When ANC is >1000 cells/mm^3, resume XELJANZ XR 11 mg once daily. UC patients: • 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 treatment with XELJANZ/XELJANZ XR

Table 6: Dose Adjustments for Anemia

Low Hemoglobin Value	
Lab Value (g/dL)	**Recommendation**
<2 g/dL decrease and ≥9.0 g/dL	Maintain dose
≥2 g/dL decrease or <8.0 g/dL (Confirmed by repeat testing)	Interrupt the administration of XELJANZ/XELJANZ XR until hemoglobin values have normalized

Table 7: Dose Adjustments for Lymphopenia Low Lymphocyte Count

Low Lymphocyte Count	
Lab Value (cells/mm^3)	**Recommendation**
Lymphocyte count greater than or equal to 500	Maintain dose
Lymphocyte count less than 500 (Confirmed by repeat testing)	Discontinue XELJANZ/XELJANZ XR

Dose Modification in Patients with Renal or Hepatic Impairment

XELJANZ

- XELJANZ is contraindicated in patients with severe hepatic impairment
- In patients with moderate (CLcr ≥30 and <60 mL/min) or severe (CLcr ≥15 and <30 mL/min) renal insufficiency (including patients with ESRD but not limited to those undergoing hemodialysis):
    - The recommended dose is XELJANZ 5 mg once daily when the indicated dose in the presence of normal renal function is XELJANZ 5 mg twice daily.
    - The recommended dose is XELJANZ 5 mg twice daily when the indicated dose in the presence of normal renal function is XELJANZ 10 mg twice daily.
    - Use XELJANZ with caution in this patient population.

    - For patients undergoing hemodialysis, dose should be administered after the dialysis session on dialysis days. If a dose was taken before the dialysis procedure, supplemental doses are not recommended in patients after dialysis.
    - Patients with severe renal insufficiency should remain on a reduced dose even after hemodialysis.
- In patients with moderate hepatic impairment:
    - The recommended dose is XELJANZ 5 mg once daily when the indicated dose in the presence of normal hepatic function is XELJANZ 5 mg twice daily.
    - The recommended dose is XELJANZ 5 mg twice daily when the indicated dose in the presence of normal hepatic function is XELJANZ 10 mg twice daily.
    - Use XELJANZ with caution in this patient population.

XELJANZ XR

- XELJANZ XR is contraindicated in patients with severe hepatic impairment and should not be used in patients with moderate hepatic impairment.
- XELJANZ XR is not recommended in patients with moderate (CLcr ≥30 and <60 mL/min), or severe (CLcr ≥15 and <30 mL/min) renal insufficiency (including patients with ESRD but not limited to those undergoing hemodialysis).

In patients with moderate hepatic impairment or moderate to severe renal insufficiency, XELJANZ 5 mg once daily may be considered.

Dose Modification Due to Drug Interactions

Coadministration of potent inducers of CYP3A4 (e.g. rifampin) with XELJANZ/XELJANZ XR may result in loss of efficacy or reduced clinical response to XELJANZ/XELJANZ XR. Coadministration of potent inducers of CYP3A4 with XELJANZ/XELJANZ XR is not recommended.

XELJANZ

- In patients receiving potent inhibitors of Cytochrome P450 3A4 (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):
    - Reduce XELJANZ dose to 5 mg twice daily in patients taking 10 mg twice daily.
    - Reduce XELJANZ dose to 5 mg once daily in patients taking 5 mg twice daily.

XELJANZ XR

- XELJANZ XR is not recommended in patients:
    - Receiving potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g ketoconazole).
    - Receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g. fluconazole).

In patients with dose modifications due to drug interactions, XELJANZ 5 mg once daily may be considered.

Special Populations

Geriatrics (>65 years)

No dosage adjustment is required in patients aged 65 years and older (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatrics (<18 years of age)

The safety and efficacy of XELJANZ/XELJANZ XR in children aged from neonates to less than 18 years of age has not yet been established. Therefore XELJANZ/XELJANZ XR should not be used in this patient population (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY**).

Missed Dose

For a missed dose, resume at the next scheduled dose.

OVERDOSAGE

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

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

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.

Pharmacodynamics

In patients with RA, treatment with XELJANZ (tofacitinib) was associated with dose-dependent reductions of circulating CD16/56+ natural killer 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 were small and inconsistent. The clinical significance of these changes is unknown.

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

After treatment with XELJANZ in patients with RA, 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.

Similar changes in T cells, B cells and serum CRP have been observed in patients with active PsA, although reversibility was not assessed. Total serum immunoglobulins were not assessed in patients with active PsA.

Patients with UC were not studied.

Pharmacokinetics (PK)

XELJANZ

Following oral administration of XELJANZ, 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 in the therapeutic dose range. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after BID administration.

A geometric mean accumulation ratio (Rac) of 1.12 following BID dosing indicates little difference between single dose and steady state concentrations as well as the predictability of steady state PK from single dose data. The dose-AUC relationship was adequately described by a linear model fit to log-both sides transformed data while the dose-C_{max} relationship were best described by a nonlinear sigmoidal, hyperbolic model fit to log-transformed C_{max} data. Although the nonlinear model provided better description of the dose-C_{max} relationship relative to a linear model, when compared to 5 mg, the mean model predicted relative changes in dose-normalized C_{max} were approximately +7% for 10 mg, +2% for 30 mg, and -10% for 50 mg doses. These small changes from linearity support the conclusion that XELJANZ C_{max} is approximately dose proportional at least up to 5 times the 10 mg dose.

XELJANZ XR

Following oral administration of XELJANZ XR, peak plasma tofacitinib concentrations are reached at 4 hours and the half-life is ~6 hours. Steady state concentrations are achieved within 48 hours with negligible accumulation (accumulation ratio: 1.12) after once daily (QD) administration. At steady state, C_{min} for XELJANZ XR 11 mg QD is approximately 29% lower

and C_{trough} is approximately 26% lower compared to XELJANZ 5 mg BID. Area under the curve (AUC) and C_{max} of tofacitinib for XELJANZ XR 11 mg administered once daily are equivalent to those of XELJANZ 5 mg administered twice daily.

Pharmacokinetics in Patients with Moderately to Severely Active UC

Population PK analysis in UC patients indicated that PK characteristics were similar to that of RA patients. There were no clinically relevant differences in tofacitinib exposure (AUC), based on age, weight, gender and race, after accounting for differences in renal function (i.e., creatinine clearance) between patients. The between-subject variability (% coefficient of variation) in AUC of tofacitinib is estimated to be approximately 23% to 25% in UC patients.

Absorption:

XELJANZ

Tofacitinib is well-absorbed, with an absolute 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, XELJANZ was administered without regard to meal.

XELJANZ XR

Coadministration of XELJANZ XR with a high-fat meal resulted in no changes in AUC while C_{max} was increased by 27% and T_{max} was extended by approximately 1 hour.

Distribution:

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

Metabolism:

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 tofacitinib, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of tofacitinib is attributed to the parent molecule.

Excretion:

Approximately 94% of a radioactive dose of XELJANZ was recovered from the urine (80%) and feces (14%), with the majority of excreted radioactivity recovered within 24 hours after dosing.

Table 8: Summary of Tofacitinib Pharmacokinetic Parameters after Repeated Oral Administration of XELJANZ 10 mg BID or Single IV Administration in Humans

	Oral Administration			IV Administration	
	C_{max} (ng/mL)	**$t_{½}$ (h)**	**$AUC_{0\text{-}12hrs}$ (ng·h/mL)**	**Clearance (L/h)**	**Volume of distribution (L)**
Healthy Volunteers	79.4	3.0	311	25	87

	Oral Administration			IV Administration	
	C_{max} (ng/mL)	$t_{½}$ (h)	$AUC_{0-12hrs}$ (ng·h/mL)	Clearance (L/h)	Volume of distribution (L)
RA Patients	116	3.62	507	N/A (no IV data)	N/A (no IV data)
PsA Patients	88.9	3.74	436	N/A (no IV data)	N/A (no IV data)
UC Patients	91	3.05	404	N/A (no IV data)	N/A (no IV data)

N/A = Not available; C_{max} = maximum plasma concentration; $t_{½}$ = terminal elimination half-life; AUC_{0-12} = area under the plasma concentration-time curve from time 0 to 12 hours post dose; CL = total systemic clearance; V_{ss} = volume of distribution at steady state.

Table 9: Summary of Tofacitinib Pharmacokinetic Parameters after Repeated Oral Administration of XELJANZ XR 11 mg QD in Humans

	C_{max} (ng/mL)	$t_{½}$ (h)	$AUC_{0-24hrs}$ (ng·h/mL)	Tmax (h)
Healthy Volunteers	38.23	5.89	269	4.0

C_{max} = maximum plasma concentration; $t_{½}$ = terminal elimination half-life; AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours post dose.

Special Populations and Conditions

Rheumatoid Arthritis and Ulcerative Colitis

Pediatrics (<18 years of age): The pharmacokinetics, safety and effectiveness of tofacitinib in pediatric patients have not been established; therefore, XELJANZ/XELJANZ XR should not be used in this patient population. Pharmacokinetic of tofacitinib was characterized in an open-label, non-randomized, multi-center, Phase 1 study conducted in pediatric patients (aged from 2 to less than 18 years) with juvenile idiopathic arthritis. A total of 26 patients were enrolled in this study and treated at dosing regimens based on the children's age and body weight. The study consisted of 3 cohorts based on subject age with at least 8 subjects per cohort. Based on limited data, the PK profile of tofacitinib appears to be characterized by a rapid absorption (peak plasma concentrations were reached within 0.5-1 hour) and a rapid elimination. The average half-lives for tofacitinib were approximately 2.6h, 1.9h, and 1.8h for the Cohorts 1 (12 to <18 years), 2 (6 to <12 years) and 3 (2 to <6 years), respectively, with individual values ranging from 1.4 to 3.1h across all cohorts.

Geriatrics (>65 years of age): Population PK analysis in RA patients indicated that elderly patients 80 years of age were estimated to have <5% higher XELJANZ AUC relative to the mean age of 55 years. Of the 3315 patients who enrolled in studies I to V, a total of 505 (15%) RA patients were 65 years of age and older, including 71 (2%) patients 75 years and older. The frequency of serious infection among XELJANZ treated subjects 65 years of age and older was higher than those under the age of 65.

There were not enough elderly patients treated with XELJANZ (n=77) in the UC program to adequately study the effects of XELJANZ in this population. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly (see **WARNINGS AND PRECAUTIONS**).

Gender: Based on population PK analysis, female RA patients were estimated to have 7% lower XELJANZ AUC compared to male RA patients. Female UC patients were estimated to have 15.2% higher XELJANZ AUC compared to male UC patients.

Race: In RA patients, no major differences (<5%) were estimated in XELJANZ AUC between White, Black and Asian RA patients by population PK analysis. In UC patients, population PK analysis indicated that Asian patients had 7.3% higher XELJANZ AUC compared to non-Asian patients. There was a higher incidence of adverse events in Asian patients. Therefore, XELJANZ/XELJANZ XR should be used with caution in Asian patients (see **WARNINGS AND PRECAUTIONS**).

Body Weight: Population PK analysis in RA patients indicated that systemic exposure (AUC) of XELJANZ in the extremes of body weight (40 kg, 140 kg) were similar to that of a 70 kg patient. An approximately 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 (% coefficient of variation) in AUC of XELJANZ is estimated to be approximately 27%. Population PK analysis in UC patients also indicated that XELJANZ AUC did not significantly change with patient body weight.

Hepatic Impairment: XELJANZ/XELJANZ XR is contraindicated in patients with severe hepatic impairment (see **CONTRAINDICATIONS**). Subjects with mild and moderate hepatic impairment had 3%, and 65% higher XELJANZ AUC, respectively, compared with healthy subjects.

No dose adjustment of XELJANZ/XELJANZ XR is required in patients with mild hepatic impairment. XELJANZ XR has not been studied in patients with moderate and severe hepatic impairment. Therefore, XELJANZ XR should not be used in patients with moderate hepatic impairment.

The recommended total daily dose in patients with moderate hepatic impairment is half the total daily dose recommended for patients with normal hepatic function. The recommended dose is XELJANZ 5 mg twice daily when the indicated dose in the presence of normal hepatic function is XELJANZ 10 mg twice daily; the recommended dose is XELJANZ 5 mg once daily when the indicated dose in the presence of normal hepatic function is XELJANZ 5 mg twice daily (see **DOSAGE AND ADMINISTRATION**).

XELJANZ/XELJANZ XR has not been studied in patients with severe hepatic impairment or in patients with positive hepatitis B virus or hepatitis C virus serology, and should not be used in these populations.

Renal Impairment: Subjects with mild, moderate, and severe renal impairment had 37%, 43% and 123% higher XELJANZ AUC, respectively, compared with healthy subjects. In subjects with ESRD undergoing hemodialysis, the contribution of dialysis to the total clearance of tofacitinib was relatively small.

In subjects with ESRD undergoing hemodialysis, mean AUC was approximately 40% higher compared with historical healthy subject data, consistent with approximately 30% contribution of renal clearance to the total clearance of tofacitinib. Dose adjustment is recommended in ESRD patients undergoing hemodialysis (see **DOSAGE AND ADMINISTRATION**).

No dose adjustment of XELJANZ/XELJANZ XR is required in patients with mild renal impairment. XELJANZ XR has not been studied in patients with moderate and severe renal impairment. Therefore, XELJANZ XR is not recommended in patients with moderate and severe renal impairment, including patients with ESRD undergoing hemodialysis.

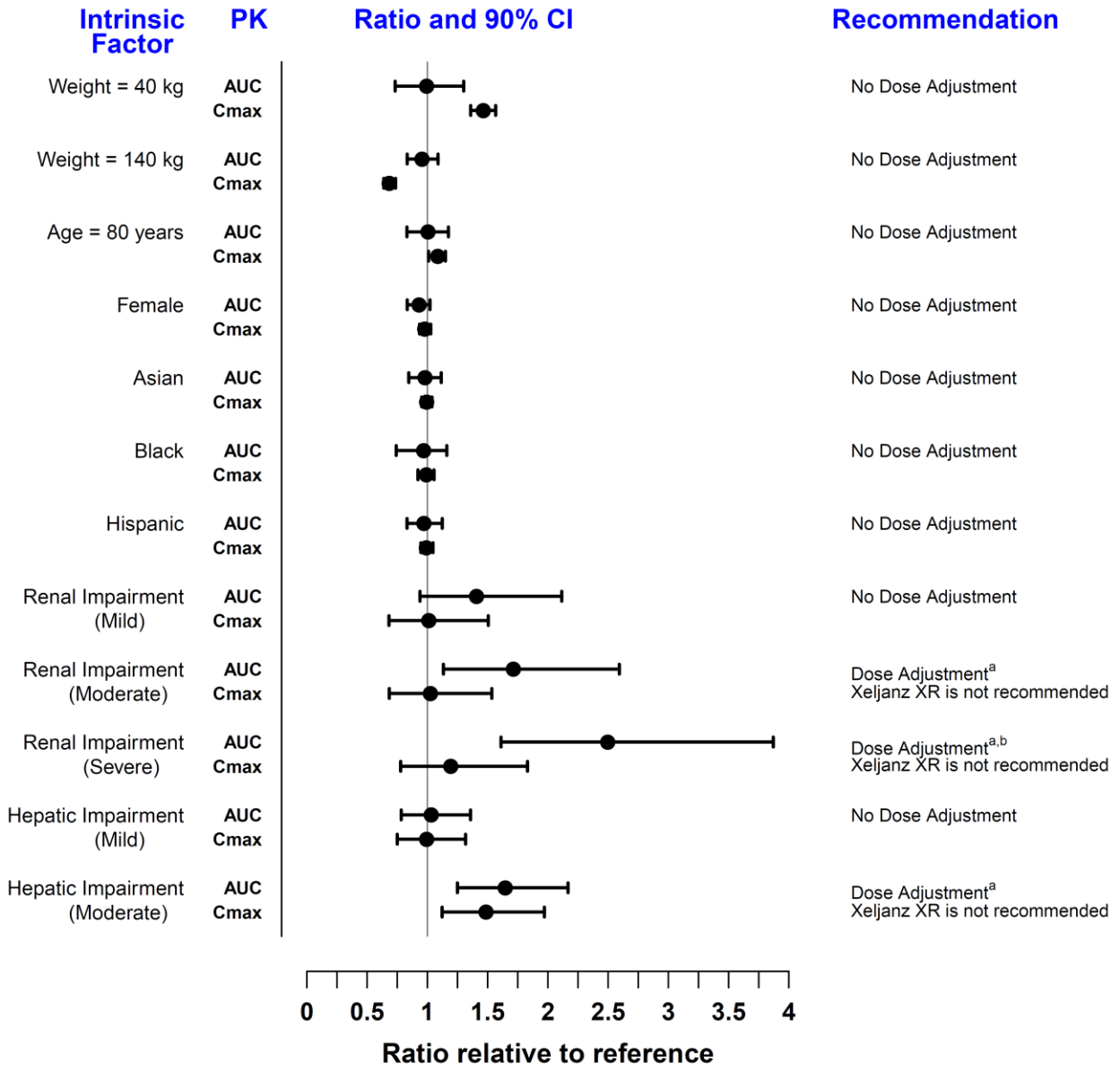
The recommended total daily dose in patients with moderate or severe renal impairment, including patients with ESRD but not limited to those undergoing hemodialysis, is half the total daily dose recommended for patients with normal renal function. The recommended dose is XELJANZ 5 mg twice daily when the indicated dose in the presence of normal renal function is XELJANZ 10 mg twice daily; the recommended dose is XELJANZ 5 mg once daily when the indicated dose in the presence of normal renal function is XELJANZ 5 mg twice daily (see **DOSAGE AND ADMINISTRATION**).

In clinical trials, XELJANZ/XELJANZ XR was not evaluated in patients with baseline creatinine clearance values (estimated by the Cockroft-Gault equation) less than 40 mL/min.

Genetic Polymorphism: Mean C_{max} and $AUC_{0-\infty}$ values of tofacitinib following administration of XELJANZ in poor metabolizers of CYP2C19 (carriers of CYP2C19*2/*2, CYP2C19*2/*3 or CYP2C19*3/*3 alleles) were approximately 15% and 17% greater, respectively, than those in normal metabolizers, indicating that CYP2C19 is a minor contributor of XELJANZ clearance.

The impact of intrinsic factors on tofacitinib following administration of XELJANZ pharmacokinetics is summarized in Figure 3 with dosage adjustment recommendations.

Figure 3: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics



PK=Pharmacokinetics; CI=Confidence Interval

Note: Reference values for weight, age, gender, and race comparisons are 70 kg, 55 years, male, and white, respectively; reference groups for renal and hepatic impairment data are subjects with normal renal and hepatic function.

[a] In RA patients the recommended dose is XELJANZ 5 mg once daily. In UC patients the recommended dose is half the total daily dose indicated for patients with normal renal and hepatic function, i.e., the recommended dose is XELJANZ 5 mg twice daily when the indicated dose in the presence of normal renal and hepatic function is XELJANZ 10 mg twice daily, and the recommended dose is XELJANZ 5 mg once daily when the indicated dose in the presence of normal renal and hepatic function is XELJANZ 5 mg twice daily.

[b] Supplemental doses are not necessary in patients after dialysis.

Psoriatic Arthritis
Results from population PK analysis in patients with active PsA were consistent with those in patients with RA.

STORAGE AND STABILITY

Store between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

XELJANZ
Tablet: 5 mg tofacitinib (as tofacitinib citrate) (White round film coated tablet with Pfizer on one side and JKI 5 on the other side)
HDPE bottles with desiccant and child-resistant caps containing 60 film-coated tablets.
Foil / foil blisters containing 56 film-coated tablets.

The tablet core contains Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. The film coat contains HPMC 2910/Hypromellose 6 cP, Lactose Monohydrate, Macrogol/PEG 3350, Titanium dioxide, Triacetin (Glycerol Triacetate)

Tablet: 10 mg (Blue round film coated tablet with Pfizer on one side and JKI 10 on the other side)
HDPE bottles with desiccant and child-resistant caps containing 60 film-coated tablets.
Foil / foil blisters containing 56 film-coated tablets.

The tablet core contains: Microcrystalline Cellulose, Lactose Monohydrate, croscarmellose Sodium, Magnesium Stearate. The film coat contains: HPMC 2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, titanium dioxide, triacetin (glycerol triacetate), FD&C blue #2/indigo carmine aluminum lake, FD&C blue #1/brilliant blue FCF aluminum lake.

XELJANZ XR
Tablets: 11 mg tofacitinib (as tofacitinib citrate) (Pink oval extended-release-coated tablets)
HDPE bottles with desiccant and child-resistant caps containing 14 or 30 extended release film-coated tablets.

The tablet core contains: sorbitol, hydroxyethyl cellulose, copovidone, magnesium stearate. The Film Coat contains cellulose acetate, hydroxypropyl cellulose, HPMC 2910/hypromellose, titanium dioxide, triacetin, red iron oxide. The Printing ink contains shellac glaze, ammonium hydroxide, propylene glycol, ferrosoferric oxide/black iron oxide.

PART II: SCIENTIFIC INFORMATION

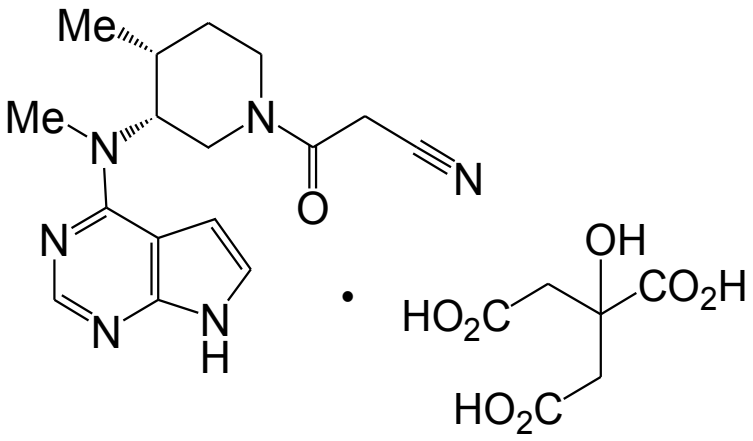
PHARMACEUTICAL INFORMATION

The active ingredient in XELJANZ (tofacitinib, CP-690,550) is the citrate salt and is designated as CP-690,550-10.

CP-690,550-10 powder is a white to off-white powder with the following chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) .

The solubility of CP-690,550-10 in water (unbuffered; pH 3.54) is 2.9 mg/mL.

CP-690,550-10 has a molecular weight of 504.5 Daltons (or 312.4 Daltons as the CP 690,550 free base) and a molecular formula of $C_{16}H_{20}N_6O \cdot C_6H_8O_7$. The chemical structure of CP-690,550-10 is:



CLINICAL TRIALS

Rheumatoid Arthritis

Description of Clinical Studies

The efficacy and safety of XELJANZ were assessed in five randomized, double-blind, multicenter studies in patients ≥18 years with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Patients had ≥6 tender and ≥6 swollen joints at randomization (≥4 swollen and ≥4 tender joints for Study II). XELJANZ, 5 or 10 mg BID, was given as monotherapy (Study I) and in combination with nonbiologic DMARDs (Study II) in patients with an inadequate response to DMARDs (nonbiologic or biologic). XELJANZ, 5 or 10 mg BID, was given in combination with methotrexate 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).

The primary endpoints for Studies I and V were the proportion of patients who achieved an ACR20 response, mean change from baseline in HAQ-DI and proportion of patients who achieved DAS28-4(ESR) less than 2.6 at Month 3. The primary endpoints for Studies II, III, and IV were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in HAQ-DI at Month 3 and proportion of patients who achieved DAS28-4(ESR) less than 2.6 at Month 6.

Baseline demographics were generally similar among the treatment groups in each study and comparable between the studies. The mean age ranged from 50 to 56 years. Most (80 to 87%) of the patients were female. With the exception of Study A3921044 (46%), the majority (55% to 86%) of the patients in each study were white. The baseline demographics in each study are shown in Table 10.

Study demographics and trial design

Table 10: Summary of patient demographics for clinical trials in RA

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Age (yrs) Mean (Range)	Female (%)	Mean Disease Duration (yrs)
Background DMARD Studies*						
A3921046 Study II Sync	MC, DB, PG, PC, R, Background DMARD 12 Months	XELJANZ: 5 mg BID, 10 mg BID Placebo → 5 mg Placebo → 10 mg NR advance to next period at 3 months, All advance to next period at 6 months	792	52.3 (18-86)	81.4	8.1-10.2
A3921064 Study III Standard	MC, DB, PG, PC, R, Background MTX 12 Months	XELJANZ: 5 mg BID, 10 mg BID Placebo → 5 mg Placebo →10 mg Adalimumab 40 mg sc QOW NR advance to next period at 3 months, All advance to next period at 6 months.	717	52.9 (18-83)	81.7	6.9-9.0
A3921044 (1-Year Analysis) Study IV Scan	MC, DB, PG, PC, R, Background MTX 24 Months	XELJANZ: 5 mg BID, 10 mg BID Placebo → 5 mg Placebo →10 mg NR advance to next period at 3 months, All advance to next period at 6 months	797	[52.0-53.7]**(18-82)	85.2	8.8-9.5
A3921032 Study V Step	MC, DB, PG, PC, R, Background MTX 6 Months	XELJANZ: 5 mg BID, 10 mg BID Placebo → XELJANZ 5 mg BID at 3 months Placebo → XELJANZ 10 mg BID at 3 months	399	55.0 (20-84)	84.0	11.2-13.0

Monotherapy Studies						
A3921045 (Study I) Solo	MC, DB, PG, PC, R 6 Months	XELJANZ 5 mg BID, 10 mg BID Placebo →5 mg XELJANZ at 3 months, Placebo → 10 mg BID XELJANZ at 3 months	610	51.8 (21-81)	86.6	7.3-8.6

*In addition to their randomized treatment, all patients in background DMARD studies also received methotrexate (specified in Studies 1032, 1044, and 1064, permitted in Study 1046) or other DMARDs, mostly methotrexate (Study 1046).
** Range of mean across treatment groups.
N = number of patients randomized, MC = multicenter, DB = double blind, PG = parallel group, PC = placebo controlled, R = randomized, NR = nonresponder (patient who failed to improve at Month 3 by at least 20% from baseline in the number of swollen and tender/painful joint count), MTX = methotrexate, DMARD = disease modifying antirheumatic drug, sc = subcutaneous, QOW = every other week, LT = long term, OL = open label.

Study Results

Clinical Response:
In Studies I and V, patients treated with 5 mg BID XELJANZ had statistically superior ACR20, ACR50, and ACR70 response rates at month 3 vs. placebo-treated patients. In Studies II, III and IV, patients treated with 5 mg BID XELJANZ had statistically superior ACR20, ACR50, and ACR70 response rates at month 3 and 6 vs placebo-treated patients (Table 11). In Studies I, II and V, improvement in ACR20 response rate vs. placebo was observed within 2 weeks. In studies II, III, and IV, ACR response rates were maintained to 12 months in XELJANZ treated patients.

The percent of ACR20 responders by visit for study IV is shown in Figure 4. Similar responses were observed in Studies I, II, III and V.

The proportion of patients with DAS28-4(ESR) less than 2.6 for each study is summarized in Table 12.

Table 11: Proportion of Patients with an ACR Response

	Percent of Patients										
	Monotherapy		**DMARD Inadequate Responders**		**MTX Inadequate Responders**			**MTX Inadequate Responders**		**TNF Inhibitor Inadequate Responders**	
	Study I (SOLO)		**Study II (SYNC)**		**Study III (Standard)**			**Study IV (SCAN)**		**Study V (STEP)**	
Response Rate	PBO N=120	XELJANZ 5 mg BID N=241	PBO + DMARD N=157	XELJANZ 5 mg BID + DMARD N=311	PBO + MTX N=106	XELJANZ 5 mg BID + MTX N=196	ADA 40mg QW + MTX N=199	PBO + MTX N=154	XELJANZ 5 mg BID + MTX N=309	PBO N=131	XELJANZ 5 mg BID + MTX N=132
ACR20†											
Month 3	27%	60%***	27%	56%***	26%	61%***	56%***	27%	56%***	24%	42%*
Month 6	NA	69%	31%	53%***	28%	52%***	47%**	25%	51%***	NA	52%
ACR50††											
Month 3	13%	31%***	10%	27%***	7%	34%***	24%***	8%	29%***	8%	27%***
Month 6	NA	42%	13%	34%***	12%	37%***	28%**	8%	32%***	NA	37%
ACR70††											
Month 3	6%	15%*	2%	8%**	2%	12%**	9%*	3%	11%**	2%	14%**
Month 6	NA	22%	3%	13%***	2%	20%***	9%*	1%	15%***	NA	16%

* *p<0.05,* XELJANZ *vs. placebo + MTX/DMARD*
** *p<0.001,* XELJANZ *vs. placebo + MTX/DMARD*
*** *p<0.0001,* XELJANZ *vs. placebo + MTX/DMARD*
† Primary endpoint, Type I error controlled
†† Secondary Endpoint, Type I error not controlled

Figure 4: Percentage of ACR20 Responders by Visit for Study IV

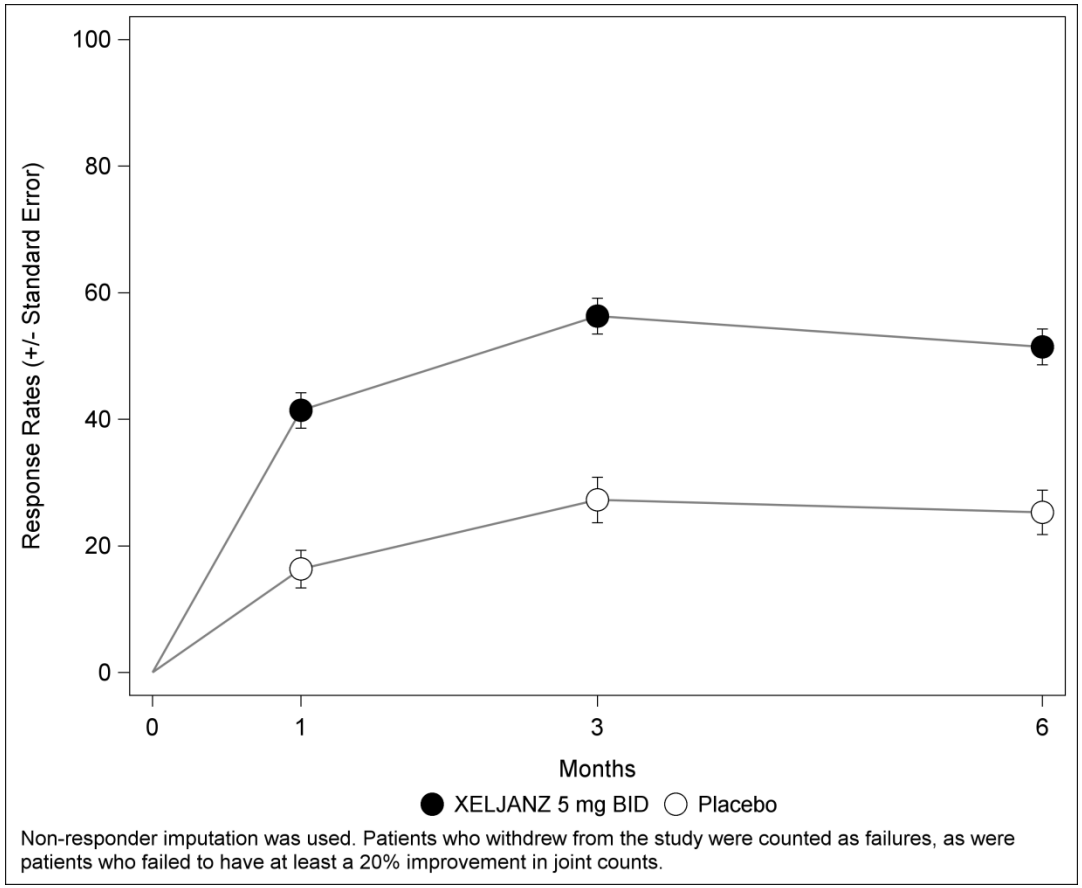


Table 12: Proportion of Patients with DAS28-4(ESR) Less Than 2.6

DAS28-4 (ESR)Less Than 2.6	Monotherapy		DMARD Inadequate Responders		MTX Inadequate Responders			MTX Inadequate Responders		TNF Inhibitor Inadequate Responders	
	Study I (SOLO)		Study II (SYNC)		Study III (Standard)			Study IV (SCAN)		Study V (STEP)	
	PBO N=122	XELJANZ 5 mg BID N=243	PBO + DMARD N=159	XELJANZ 5 mg BID + DMARD N=315	PBO + MTX N=108	XELJANZ 5 mg BID + MTX N=204	ADA 40mg QW + MTX N=204	PBO + MTX N=160	XELJANZ 5 mg BID + MTX N=321	PBO N=132	XELJANZ 5 mg BID + MTX N=133
Proportion of responders at Month 3 (n)	4% (5)	5% (13)	NA	NA	NA	NA	NA	NA	NA	2% (2)	6% (8)
Proportion of Responders at Month 6 (n)	NA	NA	3% (4)	8%* (24)	1% (1)	5% (11)	6%* (12)	1% (2)	6%†(19)	NA	NA

*Statistically significant ($p<0.05$)

†Statistical significance could not be declared in Study IV due to Step-down procedure

BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, N =number of patients, n = number of patients meeting pre-specified criteria

Physical Function Response:

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg BID demonstrated significantly greater improvement from baseline in physical functioning compared to placebo at month 3 (Studies I, II, III, and V). XELJANZ 5 mg BID 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. At month 3, patients in the XELJANZ 5 mg BID had decreases from baseline in HAQ-DI values (Table 13) which were not less than those of adalimumab-treated patients.

Table 13: Mean Change from Baseline in HAQ-DI

	Monotherapy		DMARD Inadequate Responders		MTX Inadequate Responders			MTX Inadequate Responders		TNF Inhibitor Inadequate Responders	
	Study I (SOLO)		Study II (SYNC)		Study III (Standard)			Study IV (SCAN)		Study V (STEP)	
LS Mean Change in HAQ-DI	PBO N=109	XELJANZ 5 mg BID N=237	PBO + DMARD N=147	XELJANZ 5 mg BID + DMARD N=292	PBO + MTX N=98	XELJANZ 5 mg BID + MTX N=188	ADA 40mg QW + MTX N=190	PBO + MTX N=146	XELJANZ 5 mg BID + MTX N=294	PBO N=118	XELJANZ 5 mg BID + MTX N=117
Month 3*	-0.22	-0.51***	-0.21	-0.47***	-0.25	-0.56***	-0.51***	-0.15	-0.4†	-0.18	-0.43**

* Primary efficacy time point
** *p<0.001,* XELJANZ *vs. placebo + MTX/DMARD*
*** *p<0.0001,*-XELJANZ *vs. placebo + MTX/DMARD*
† Statistical significance could not be declared in Study IV due to Step-down procedure
BID = twice daily, CI = confidence interval, FAS = full analysis set, LS = least squares, N = number of patients.
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.

Psoriatic Arthritis

Description of Clinical Studies

The efficacy and safety of XELJANZ were assessed in 2 multicenter, randomized, double-blind, placebo-controlled trials in 816 patients 18 years of age and older with active psoriatic arthritis. All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender/painful joints and at least 3 swollen joints at screening and baseline, and active plaque psoriasis at screening. Patients with different psoriatic arthritis subtypes (not mutually exclusive) were enrolled across the 2 clinical trials, including <5 joints or asymmetric involvement (21%), ≥5 joints involved (90%), distal interphalangeal (DIP) joint involvement (61%), arthritis mutilans (8%), enthesitis (80%), dactylitis (53%), total psoriatic body surface area (BSA) >3% (69%), and spondylitis (19%). Patients in these clinical trials had a diagnosis of psoriatic arthritis for a median of 5.5 years (median range 3.0-6.0 years). Of the study population randomized in the double-blind, controlled clinical studies, 54.2% were female and 94.6% were white. The mean age was 48.9 years; 77 (9.4%) patients were 65 years of age or older. All patients were required to receive treatment with a stable dose of a conventional synthetic DMARD (csDMARD; 78% received methotrexate, 13% received sulfasalazine, 7% received leflunomide, 1% received other csDMARDs) and were allowed to receive a stable low dose of oral corticosteroids (21% received equivalent to ≤10 mg/day of prednisone) and/or nonsteroidal anti-inflammatory drugs (NSAIDs; 57% received). In both clinical trials, the primary endpoints were the ACR20 response and the change in HAQ-DI at Month 3.

Study PsA-I (A3921091) was a 12-month clinical trial in 422 patients who had an inadequate response to a csDMARD (67% and 33% were inadequate responders to 1 csDMARD and ≥2 csDMARDs, respectively) and who were naïve to treatment with a TNF-inhibitor biologic DMARD (TNFi). Patients were randomized in a 2:2:2:1:1 ratio to receive XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, adalimumab 40 mg subcutaneously once every 2 weeks, placebo to XELJANZ 5 mg twice daily treatment sequence, or placebo to XELJANZ 10 mg twice daily treatment sequence, respectively; study drug was added to background csDMARD treatment. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a predetermined XELJANZ dose of 5 mg or 10 mg twice daily. Study PsA-I was not designed to demonstrate non-inferiority or superiority to adalimumab.

Study PsA-II (A3921125) was a 6-month clinical trial in 394 patients who had an inadequate response to at least 1 approved TNFi (66%, 19% and 15% were inadequate responders to 1 TNFi, 2 TNFi, and ≥3 TNFi, respectively). Patients were randomized in a 2:2:1:1 ratio to receive XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, placebo to XELJANZ 5 mg twice daily treatment sequence, or placebo to XELJANZ 10 mg twice daily treatment sequence, respectively; study drug was added to background csDMARD treatment. At the Month 3 visit, placebo patients were advanced in a blinded fashion to a predetermined XELJANZ dose of 5 mg or 10 mg twice daily as in Study PsA-I.

Study Results

Clinical Response:

Signs and symptoms

At Month 3, patients treated with XELJANZ 5 mg twice daily had higher ($p \leq 0.05$) response rates versus placebo for ACR20, ACR50, and ACR70 in Study PsA-I and for ACR20 and ACR50 in Study PsA-II; ACR70 response rate was also higher for XELJANZ 5 mg twice daily versus placebo in Study PsA-II, although the difference versus placebo was not statistically significant ($p > 0.05$) (Table 14).

Table 14: Proportion (%) of PsA Patients Who Achieved Clinical Response and Mean Change from Baseline in PsA-I and PsA-II Studies

	Conventional Synthetic DMARD Inadequate Responders[a] (TNFi-Naïve)			TNFi Inadequate Responders[b]	
	Study PsA-I			Study PsA-II[c]	
Treatment Group	**Placebo**	**XELJANZ 5 mg Twice Daily**	**Adalimumab 40 mg SC q2W[f]**	**Placebo**	**XELJANZ 5 mg Twice Daily**
N	105	107	106	131	131
ACR20					
Month 3	33%	50%*	52%	24%	50%***
Month 6	NA	59%	64%	NA	60%
Month 12	NA	68%	60%	-	-
ACR50					
Month 3	10%	28%**	33%	15%	30%*
Month 6	NA	38%	42%	NA	38%
Month 12	NA	45%	41%	-	-
ACR70					
Month 3	5%	17%*	19%	10%	17%
Month 6	NA	18%	30%	NA	21%
Month 12	NA	23%	29%	-	-
ΔLEI[d]					
Month 3	-0.4	-0.8	-1.1	-0.5	-1.3
Month 6	NA	-1.3	-1.3	NA	-1.5
Month 12	NA	-1.7	-1.6	-	-
ΔDSS[d]					
Month 3	-2.0	-3.5	-4.0	-1.9	-5.2
Month 6	NA	-5.2	-5.4	NA	-6.0
Month 12	NA	-7.4	-6.1	-	-
PASI75[e]					
Month 3	15%	43%***	39%	14%	21%
Month 6	NA	46%	55%	NA	34%
Month 12	NA	56%	56%	-	-

* $p \leq 0.05$; ** $p < 0.001$; *** $p < 0.0001$ for active treatment versus placebo at Month 3 achieved statistical significance; with the correction for type 1 error.

Abbreviations: BSA=body surface area; ΔLEI=change from baseline in Leeds Enthesitis Index; ΔDSS=change from baseline in Dactylitis Severity Score; ACR20/50/70=American College of Rheumatology ≥20%, 50%, 70% improvement; csDMARD=conventional synthetic disease-modifying antirheumatic drug; N=number of randomised and treated patients; NA=Not applicable, as data for placebo treatment is not available beyond Month 3 due to placebo advanced to XELJANZ

5 mg twice daily or XELJANZ 10 mg twice daily; SC q2w=subcutaneously once every 2 weeks; TNFi=tumour necrosis factor inhibitor; PASI=Psoriasis Area and Severity index; PASI75= ≥75% improvement in PASI.

[a] Inadequate response to at least 1 csDMARD due to lack of efficacy and/or intolerability.

[b] Inadequate response to a least 1 TNFi due to lack of efficacy and/or intolerability.

[c] Study PsA-II had a duration of 6 months.

[d] Statistical significance cannot be claimed for these endpoints based on step-down testing procedure. Baseline score was >0 in these patients.

[e] For patients with Baseline BSA ≥3% and PASI >0.

[f] Arm is not controlled for type 1 error

As with the ACR responses, in patients treated with XELJANZ 5 mg twice daily in Studies PsA-I and PsA-II, each of the components of the ACR response was consistently improved from baseline at Month 3 including tender/painful and swollen joint counts, patient assessment of arthritis pain, patient and physician's global assessment of arthritis, HAQ-DI, and CRP compared to patients receiving placebo (Table 15).

Table 15: Components of ACR Response at Baseline and Month 3 in Studies PsA-I and PsA-II

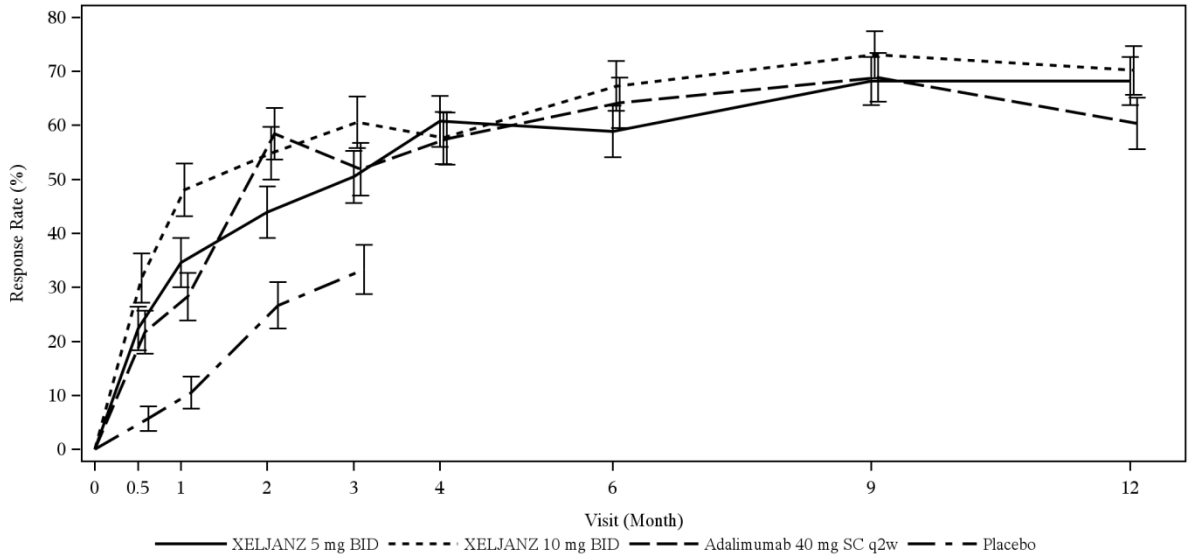
	Conventional Synthetic DMARD Inadequate Responders (TNFi-Naïve)			TNFi Inadequate Responders	
	Study PsA-I			Study PsA-II	
Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	Adalimumab 40 mg SC q2W	Placebo	XELJANZ 5 mg Twice Daily
N at Baseline	105	107	106	131	131
ACR Component[a]					
Number of tender/painful joints (0-68)					
Baseline	20.6	20.5	17.1	19.8	20.5
Month 3	14.6	12.2	10.8	15.1	11.5
Number of swollen joints (0-66)					
Baseline	11.5	12.9	9.8	10.5	12.1
Month 3	7.1	6.3	4.0	7.7	4.8
Patient assessment of arthritis pain[b]					
Baseline	53.2	55.7	50.7	54.9	56.4
Month 3	44.7	34.7	32.5	48.0	36.1
Patient global assessment of arthritis[b]					
Baseline	53.9	54.7	50.6	55.8	57.4
Month 3	44.4	35.5	32.9	49.2	36.9
HAQ-DI[c]					
Baseline	1.11	1.16	1.10	1.25	1.26
Month 3	0.95	0.81	0.75	1.09	0.88
Physician's Global Assessment of Arthritis[b]					
Baseline	53.8	54.6	50.5	53.7	53.5
Month 3	35.4	29.5	26.3	36.4	27.0
CRP (mg/L)					
Baseline	10.4	10.5	14.3	12.1	13.8
Month 3	8.60	4.02	3.10	11.44	7.72

[a] Data shown are mean value at baseline and at Month 3
[b] Visual analog scale (VAS): 0 = best, 100 = worst
[c] HAQ-DI = Health Assessment Questionnaire – Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities

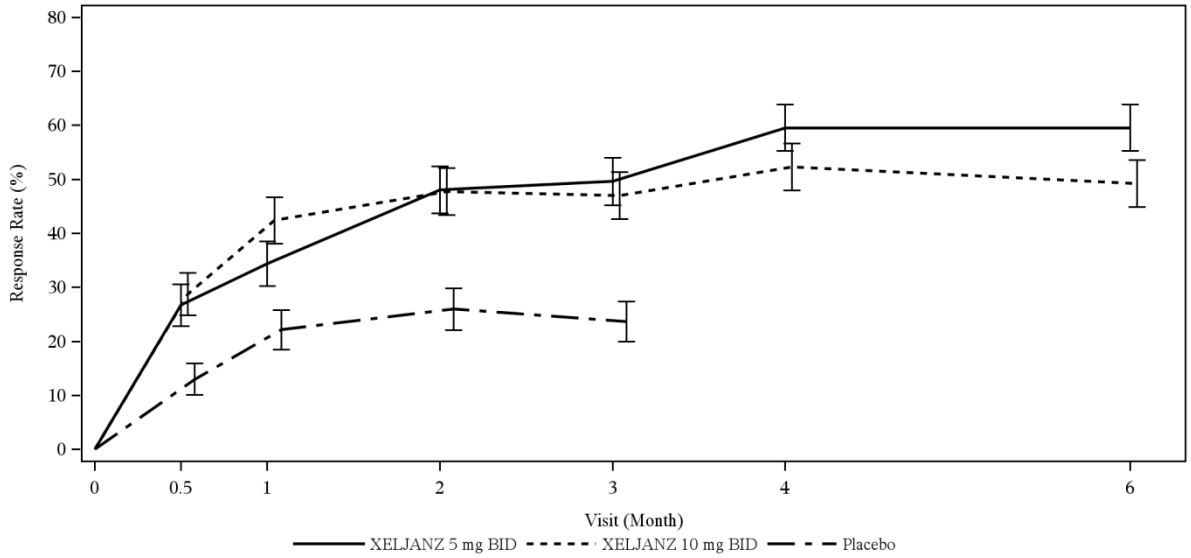
The percentage of ACR20 responders by visit for Studies PsA-I and PsA-II is shown in Figure 5. In XELJANZ-treated patients in both Studies PsA-I and PsA-II, significantly higher ACR20 response rates were observed within 2 weeks compared to placebo (Figure 5).

Figure 5: Percentage of ACR20 Responders by Visit

a) Through Month 12 in Study PsA-I



b) Through Month 6 in Study PsA-II[a]



In Studies PsA-I and PsA-II, the comparison of XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and adalimumab (Study PsA-I only) to placebo was significant (p-value ≤0.05) at Months 0.5, 1, 2, and 3.
BID = twice daily; SC q2w = subcutaneously once every 2 weeks.
Patients randomized to placebo treatment were advanced to either XELJANZ 5 mg or 10 mg twice daily in a blinded manner at Month 3; results for the XELJANZ portion of the placebo→XELJANZ treatment sequence (i.e., post-Month 3) are not included in the figure to improve readability.
[a] Study PsA-II had a duration of 6 months.

Physical Function:

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg twice daily demonstrated greater improvement (p≤0.05) from baseline in physical functioning compared to placebo at Month 3 (Table 16).

Table 16: Change from Baseline in HAQ-DI in Studies PsA-I and PsA-II

	Least Squares Mean Change From Baseline in HAQ-DI				
	Conventional Synthetic DMARD Inadequate Responders[a] (TNFi-Naïve)			TNFi Inadequate Responders[b]	
	Study PsA-I			Study PsA-II	
Treatment Group	**Placebo**	**XELJANZ 5 mg Twice Daily**	**Adalimumab 40 mg SC q2W[c]**	**Placebo**	**XELJANZ 5 mg Twice Daily**
N	104	107	106	131	129
Month 3	-0.18	-0.35*	-0.38	-0.14	-0.39***
Month 6	NA	-0.45	-0.43	NA	-0.44
Month 12	NA	-0.54	-0.45	NA	NA

* $p \leq 0.05$; *** $p < 0.0001$ for active treatment versus placebo at Month 3 achieved statistical significance; with the correction for type 1 error.

Abbreviations: DMARD=disease-modifying antirheumatic drug; HAQ-DI=Health Assessment Questionnaire Disability Index; N=total number of patients in the statistical analysis; SC q2w=subcutaneously once every 2 weeks; TNFi=tumour necrosis factor inhibitor; NA=Not applicable, as data for placebo treatment is not available beyond Month 3 due to placebo advanced to XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily.

[a] Inadequate response to at least one conventional synthetic DMARD (csDMARD) due to lack of efficacy and/or intolerability.

[b] Inadequate response to a least one TNF inhibitor (TNFi) due to lack of efficacy and/or intolerability.

[c] Arm is not controlled for type 1 error

The HAQ-DI responder rate (response defined as having decrease from baseline of ≥0.35) at Month 3 in Studies PsA-I and PsA-II was 53% and 50% , respectively in patients receiving XELJANZ 5 mg twice daily, 31% and 28%, respectively in patients receiving placebo, and 53% in patients receiving adalimumab 40 mg subcutaneously once every 2 weeks (Study PsA-I only).

Ulcerative Colitis

Description of Clinical Studies

The efficacy and safety of XELJANZ for the treatment of adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore ≥2 and rectal bleeding subscore ≥1) were assessed in 3 multicentre, double blind, randomised, placebo controlled studies: 2 identical induction studies OCTAVE Induction 1 and OCTAVE Induction 2 followed by 1 maintenance study OCTAVE Sustain. Enrolled patients had failed at least one conventional therapy, including corticosteroids, immunomodulators, and/or a TNF inhibitor. Concomitant stable doses of oral aminosalicylates and corticosteroids (prednisone daily dose up to 25 mg equivalent) were permitted with taper of corticosteroids to discontinuation mandated within 15 weeks of entering the maintenance study. XELJANZ was administered as monotherapy (i.e., without concomitant use of biologics and immunosuppressants) for ulcerative colitis.

Table 17: Phase 3 Clinical Trials of Tofacitinib 5 and 10 mg Twice Daily Doses in Patients with UC

Studies	OCTAVE Induction 1 (A3921094)	OCTAVE Induction 2 (A3921095)	OCTAVE Sustain (A3921096)
Treatment groups (Randomisation ratio)	XELJANZ 10 mg twice daily Placebo (4:1)	XELJANZ 10 mg twice daily Placebo (4:1)	XELJANZ 5 mg twice daily XELJANZ 10 mg twice daily Placebo (1:1:1)
Number of patients enrolled	598	541	593
Study duration	8 weeks	8 weeks	52 weeks
Primary efficacy endpoints	Remission	Remission	Remission
Key secondary efficacy endpoints	Improvement of endoscopic appearance of the mucosa	Improvement of endoscopic appearance of the mucosa	Improvement of endoscopic appearance of the mucosa Sustained corticosteroid-free remission among patients in remission at baseline
Prior TNFi failure	51.3%	52.1%	44.7%
Prior corticosteroid failure	74.9%	71.3%	75.0%
Prior immunosuppressant failure	74.1%	69.5%	69.6%
Baseline corticosteroid use	45.5%	46.8%	48.7%

TNFi=tumour necrosis factor inhibitor

In addition, an open-label long-term extension study (OCTAVE Open) was also performed (see further down for more information)

Induction Efficacy Data (OCTAVE Induction 1 and OCTAVE Induction 2):
The primary endpoint of OCTAVE Induction 1 and OCTAVE Induction 2 was the proportion of patients in remission at Week 8 (i.e., a total Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0). The key secondary endpoint was the proportion of patients with improvement of endoscopic appearance of the mucosa at Week 8. (i.e., endoscopy subscore of 0 or 1). Central endoscopy readings were used for these endpoints.

A significantly greater proportion of patients treated with XELJANZ 10 mg twice daily achieved remission and improvement of endoscopic appearance of the mucosa at Week 8 compared to placebo in both studies, as shown in Table 18.

Table 18: Proportion of Patients Meeting Efficacy Endpoints at Week 8 (OCTAVE Induction 1 and OCTAVE Induction 2, Central Endoscopy Read)

	OCTAVE Induction 1		
Endpoint	**Placebo**	**XELJANZ 10 mg Twice daily**	**Difference Between XELJANZ 10 mg Twice Daily and Placebo (95% CI)**
	N=122	**N=476**	
Remission[a]	8.2%	18.5%	10.3 (4.3, 16.3)‡
Improvement of endoscopic appearance of the mucosa[b]	15.6%	31.3%	15.7 (8.1, 23.4)†
	OCTAVE Induction 2		
Endpoint	**Placebo**	**XELJANZ 10 mg Twice daily**	**Difference Between XELJANZ 10 mg Twice Daily and Placebo (95% CI)**
	N=112	**N=429**	
Remission[a]	3.6%	16.6%	13.0 (8.1, 17.9)†
Improvement of endoscopic appearance of the mucosa[b]	11.6%	28.4%	16.8 (9.5, 24.1)†

† $p<0.001$; ‡ $p<0.05$.

N=number of patients in the analysis set.

a. Primary endpoint: Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore > 1) and rectal bleeding subscore of 0.

b. Key secondary endpoint: improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).

In both subgroups of patients with or without prior TNF inhibitor failure, a greater proportion of patients treated with XELJANZ 10 mg twice daily achieved remission and improvement of endoscopic appearance of the mucosa at Week 8 as compared to placebo. This treatment difference was consistent between the 2 subgroups (Table 19).

Table 19: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 8 by TNF Inhibitor Therapy Subgroups (OCTAVE Induction 1 and OCTAVE Induction 2 Central Endoscopy Read)

OCTAVE Induction 1 (A3921094)		
Endpoint	**Placebo N=122**	**XELJANZ 10 mg twice daily N=476**
Remission at Week 8[a]		
With prior TNF inhibitor failure	1.6% (1/64)	11.1% (27/243)
Without prior TNF inhibitor failure[b]	15.5% (9/58)	26.2% (61/233)
Improvement of endoscopic appearance of the mucosa at Week 8[c]		
With prior TNF inhibitor failure	6.3% (4/64)	22.6% (55/243)
Without prior TNF inhibitor failure[b]	25.9% (15/58)	40.3% (94/233)

OCTAVE Induction 2 (A3921095)		
Endpoint	**Placebo N=112**	**XELJANZ 10 mg twice daily N=429**
Remission at Week 8[a]		
With prior TNF inhibitor failure [d]	0.0% (0/60)	11.7% (26/222)
Without prior TNF inhibitor failure[b]	7.7% (4/52)	21.7% (45/207)
Improvement of endoscopic appearance of the mucosa at Week 8[c]		
With prior TNF inhibitor failure [d]	6.7% (4/60)	21.6% (48/222)
Without prior TNF inhibitor failure[b]	17.3% (9/52)	35.7% (74/207)

TNF=tumour necrosis factor; N=number of patients in the analysis set.

a. Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.

b. Failed one or more conventional therapies (corticosteroid, azathioprine, 6-mercaptopurine) but did not have history of prior failure of TNF inhibitor therapy.

c. Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).

d Inadequate response, loss of response, or intolerance to TNF inhibitor therapy.

Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in patients treated with XELJANZ.

Clinical response was defined as a decrease from baseline in Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the subscore for rectal bleeding of ≥1 point or absolute subscore for rectal bleeding of 0 or 1. Clinical response was observed in 60% of patients treated with XELJANZ 10 mg twice daily compared to 33% of placebo patients in Octave Induction 1 and 55% compared to 29% in Octave Induction 2.

Maintenance (OCTAVE Sustain):
A total of 593 patients who completed 8 weeks in one of the induction studies and achieved clinical response were re-randomized into OCTAVE Sustain; 179 out of 593 (30%) patients were in remission at baseline of OCTAVE Sustain.

The primary endpoint was the proportion of patients in remission at Week 52. The 2 key secondary endpoints were the proportion of patients with improvement of endoscopic appearance of the mucosa at Week 52, and the proportion of patients with sustained corticosteroid-free remission at both Week 24 and Week 52 among patients in remission at baseline of OCTAVE Sustain.

A significantly greater proportions of patients in both the XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily treatment groups achieved the primary and two key secondary endpoints, as shown in Table 20.

Table 20: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 52 (Maintenance OCTAVE Sustain, Central Endoscopy Read)

Endpoint	**Placebo N=198**	**XELJANZ 5 mg twice daily N=198**	**Difference Between XELJANZ 5 mg Twice Daily and Placebo (95% CI)**	**XELJANZ 10 mg twice daily N=197**	**Difference Between XELJANZ 10 mg Twice Daily and Placebo (95% CI)**
Remission[a]	11.1%	34.3%	23.2 (15.3, 31.2)*	40.6%	29.5 (21.4, 37.6)*
Improvement of endoscopic appearance of the mucosa[b]	13.1%	37.4%	24.2 (16.0, 32.5)*	45.7%	32.6 (24.2, 41.0)*
Sustained corticosteroid-free remission at both Week 24 and Week 52 among patients in remission at baseline[c]	N = 59 5.1%	N = 65 35.4%	30.3 (17.4, 43.2)*	N = 55 47.3%	42.2 (27.9, 56.5)*

* $p<0.0001$

N=number of patients in the analysis set.

a. Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.

b. Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).

c. Sustained corticosteroid-free remission was defined as being in remission and not taking corticosteroids for at least 4 weeks prior to the visit at both Week 24 and Week 52.

Additionally, among the 179 patients in remission at baseline (59 in the placebo group, 65 in the XELJANZ 5 mg BID group, and 55 in the XELJANZ 10 BID group), the rate of patients with remission at week 52 (i.e., maintained remission) was larger with XELJANZ 5 mg BID (46%) and 10 mg BID (56%) as compared to placebo (10%).

In both subgroups of patients with or without prior TNF inhibitor failure, the proportions of patients treated with either XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily were numerically larger as compared to placebo for the primary and key secondary endpoints, however, statistical significance was not possible to determine (see Table 21).

Table 21: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints in Maintenance Study OCTAVE Sustain (A3921096) by TNF Inhibitor Therapy Subgroup (Central Endoscopy Read)

Endpoint	Placebo N=198	XELJANZ 5 mg twice daily N=198	XELJANZ 10 mg twice daily N=197
Remission at Week 52[a]			
With prior TNF inhibitor failure[e]	10/89 (11.2%)	20/83 (24.1%)	34/93 (36.6%)
Without prior TNF inhibitor failure[b]	12/109 (11.0%)	48/115 (41.7%)	46/104 (44.2%)
Improvement of endoscopic appearance of the mucosa at Week 52[c]			
With prior TNF inhibitor failure[e]	11/89 (12.4%)	25/83 (30.1%)	37/93 (39.8%)
Without prior TNF inhibitor failure[b]	15/109 (13.8%)	49/115 (42.6%)	53/104 (51.0%)
Sustained corticosteroid-free remission at both Week 24 and Week 52 among patients in remission at baseline[d]			
With prior TNF inhibitor failure[e]	1/21 (4.8%)	4/18 (22.2%)	7/18 (38.9%)
Without prior TNF inhibitor failure[b]	2/38 (5.3%)	19/47 (40.4%)	19/37 (51.4%)

TNF=tumour necrosis factor; N=number of patients in the analysis set.

a. Remission was defined a Mayo score ≤2 with no individual subscore >1, and rectal bleeding subscore of 0

b. Patients who failed ≥1 conventional therapies (corticosteroid, azathioprine, 6-mercaptopurine) but did not have history of prior failure of TNF inhibitor therapy.

c. Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).

d. Sustained corticosteroid-free remission was defined as being in remission and not taking corticosteroids for at least 4 weeks prior to the visit at both Week 24 and Week 52.

e. Prior TNF inhibitor failure was defined in this program as inadequate response, loss of response, or intolerance to TNF inhibitor therapy.

Open-label Extension Study (OCTAVE Open):
Patients who did not achieve clinical response in one of the induction studies (Study OCTAVE Induction 1 or OCTAVE Induction 2) after 8 weeks of XELJANZ 10 mg twice daily, were allowed to enter an open-label extension study (OCTAVE Open). After an additional 8 weeks of XELJANZ 10 mg twice daily in Study OCTAVE Open, 53% (155/293) patients achieved clinical response and 14% (42/292) patients achieved remission.

TOXICOLOGY

Single and Repeat-Dose Toxicity

Tofacitinib caused death in rats at single oral doses of ≥500 mg/kg. Single intravenous doses up to 3 mg/kg did not induce local or systemic toxicity in rats. In cynomolgus monkeys emesis and decreased activity were observed at single oral doses of ≥200 mg/kg (divided 3 times daily [TID], ~7 hours apart).

Immune and hematopoietic organ systems were identified as main targets in repeat-dose toxicity studies. Effects on the immune system (including decreased circulating lymphocytes, lymphoid depletion of lymph nodes, spleen, thymus and bone marrow, and bacterial and viral infections) were consistent with inhibition of JAK1/3. Decreases in hemoglobin, hematocrit, erythrocyte numbers and reticulocytes were attributed to JAK2 inhibition. These effects were generally reversible during a 4-week recovery phase in the 4- and 6-week monkey and rat studies,

respectively. Repeated oral doses up to 10 mg/kg once daily in rats (up to approximately 15 or 7.6 times human clinical exposure at 5 or 10 mg BID) and 1 mg/kg twice daily in adult cynomolgus monkeys (approximately 1 or 0.5 times human exposure at 5 or 10 mg BID) were tolerated in studies up to 6 months and 39 weeks duration, respectively. In the 39-week juvenile monkey study, the T-dependent antibody response to antigen immunization was decreased at the high dose of 5 mg/kg twice daily, approximately 5 or 2.5 times human exposure at 5 or 10 mg BID.

Mutagenesis

Tofacitinib was not mutagenic in the bacterial reverse mutation assay. Reproducible increases in chromosomal abnormalities were observed in a human lymphocyte *in vitro* cytogenetic assay, at high cytotoxic concentrations with metabolic activation, but no effects were observed without metabolic activation. In follow up studies, tofacitinib was not mutagenic in mammalian cells (*in vitro* CHO/HGPRT assay) and did not induce primary DNA damage in an *in vivo/in vitro* rat hepatocyte unscheduled DNA synthesis assay. Tofacitinib was also negative in the *in vivo* rat micronucleus test.

Carcinogenesis

In the 39-week repeat-dose toxicity study in adult monkeys, lymphomas were observed at the high dose of 5 mg/kg twice daily (approximately 6 times human exposure at 5 mg BID, or approximately 3 times the 10 mg twice daily dose), but not at the lower dose of 1 mg/kg twice daily (approximately 1 times human exposure at 5 mg BID, or approximately 0.5 times the 10 mg twice daily dose). No treatment-related tumors were observed in a 6-month rasH2 transgenic mouse study up to the high dose of 200 mg/kg/day, approximately 38 or 19 times human exposure at 5 or 10 mg BID.

In a 2-year rat carcinogenicity study, tofacitinib induced benign Leydig cell tumors and malignant hibernomas (tumors of brown adipose tissue) at oral doses of ≥30 mg/kg/day (≥35 times or 17 times human exposure at 5 or 10 mg BID) and benign thymomas at 100/75 mg/kg/day (approximately 187 or 94 times human exposure at 5 or 10 mg BID). No treatment-related tumors were found in rats at 10 mg/kg/day (approximately 16 or 8 times human exposure at 5 or 10 mg BID). The relevance of benign Leydig cell tumors to human risk is unknown.

Developmental and Reproductive Toxicity

Tofacitinib had no effect on fertility of male rats; however, in treated female rats tofacitinib decreased pregnancy rate, numbers of corpora lutea, implantation sites, and viable fetuses, with an increase in early resorptions at oral doses of ≥10 mg/kg/day (≥15 or 8 times human exposure at 5 or 10 mg BID). The non-observed-adverse-effect-level (NOAEL) for female fertility and early embryonic development was 1 mg/kg/day (approximately 1 or 0.6 times human exposure at 5 or 10 mg BID).

Tofacitinib was teratogenic (external, visceral and skeletal abnormalities) in rabbits and rats at oral doses of 30 and 100 mg/kg/day (approximately 13/6 and 146/73 times human exposure at 5/10 mg BID), respectively. In rabbits, teratogenic effects occurred in the absence of maternal toxicity, consisted of thoracogastroschisis, omphalocele, craniofacial malformations (microstomia, microphthalmia, and cleft lip and palate), membranous ventricular septal defects, gallbladder agenesis, short or absent tail, and skeletal malformations (fused sternebrae and vertebral and/or rib

anomalies). In addition, there was an increase in postimplantation loss (early and late resorptions) and consequently, reduced number of viable fetuses. The developmental NOAEL in rabbits was 10 mg/kg/day (approximately 3 or 1.5 times human exposure at 5 or 10 mg BID). In rats, tofacitinib increased postimplantation loss (early and late resorptions), reduced fetal body weights, and increased incidences of fetal malformations at doses that induced maternal toxicity. Malformations suggestive of teratogenicity included anasarca, membranous ventricular septal defects, and skeletal abnormalities (absent cervical arch, bent limb bones, hemicentric thoracic centrum, and rib and sternal anomalies). The developmental NOAEL in rats was 30 mg/kg/day (approximately 58 or 29 times human exposure at 5 or 10 mg BID).

In the peri/postnatal development study in rats, tofacitinib decreased the number of delivered and live born pups, and reduced pup survival at oral doses of 50 mg/kg/day (approximately 73 or 36 times human exposure at 5 or 10 mg BID). There was no effect on sexual maturation, or the ability of these F1 generation rats to learn, mate and produce viable F2 generation fetuses of treatment of the dams at oral doses up to 10 mg/kg/day (up to 15 or 8 times human exposure at 5 or 10 mg BID).

Table 22: Summary of Toxicology Studies

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
Single-Dose Toxicity					
Single-Dose Oral Toxicity Study in Sprague-Dawley Rats (01-2063-07)	Single Dose	Rat/ Sprague-Dawley	3M, 3F	0, 500, 1000, 2000 (Oral gavage, 20 mL/kg, 0.5% Methylcellulose/ Suspension)	**500 mg/kg:** 1 female died on Day 1; red-stained fur (nose/muzzle); ↓ eosinophils, ↓ fibrinogen, ↑ ALT, ↑ AST, ↑ glucose, ↑ BUN. **≥500 mg/kg:** ↓ activity, lethargy, partially closed eyes, labored respiration, salivation; lympho-cytolysis in mesenteric lymph node and decreased numbers of lymphocytes within the minimal zone of the splenic white pulp. **1000 mg/kg:** 6/6 animals died by Day 2; necrosis of centrilobular hepatocytes. **≥1000 mg/kg:** lacrimation and cold to touch; stomach distension; necrosis of individual hepatocytes; lymphocytolysis within the splenic white pulp. **2000 mg/kg:** 6/6 animals died by Day 2; slow respiration and eye staining/nasal discharge.
Single-Dose IV Toxicity Study in Rats with a 14-Day Recovery (09GR453)	Single Dose	Rat/Sprague-Dawley	10M, 10F[b]	0, 0.5, 1, 3 (IV, 0.5-3 mL/kg, 10mM Lactic acid in normal saline)	**≤3 mg/kg:** None
Single-Day Oral Toxicity Study in Cynomolgus Monkeys (00-2063-04)	1 Day	Monkey/ Cynomolgus	2M, 2F	40, 200, 1000[c] (Oral gavage, 7 mL/kg, 0.5% Methylcellulose/Suspension	**≥200 mg/kg:** Emesis, ↓ activity
Repeat-Dose Toxicity					
Pivotal Studies					
6-Week Oral Toxicity Study with 1-Month Recovery in Sprague-Dawley Rats (01-2063-06)	6 Weeks	Rat/Sprague-Dawley	10-15/sex/dose	1, 10, 100 Oral gavage, QD, 10 mL/kg (0.5% Methylcellulose/ Suspension	**1 mg/kg/day (LOEL):** ↓ WBC count, ↓ lymphocytes, ↓ eosinophils, ↓ basophils, ↓ RBC count, ↓ HCT, ↓ HGB, lymphoid depletion in bone marrow. **10 mg/kg/day**: Same as above, + ↓ reticulocytes, lymphoid depletion in spleen, thymus, and mesenteric lymph node. **100 mg/kg/day**: Same as above, + ↑ neutrophils, ↑ AST.

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
					100 mg/kg/day (Recovery): Recovery of reticulocytes and AST, no microscopic findings in lymphoid tissues, partial recovery of WBC count, lymphocytes, RBC parameters, and lymphoid cells in bone marrow.
6-Month Oral Toxicity Study in Rats (77435)	6 Months	Rat/Sprague-Dawley	15/sex/dose	1, 10, 100 (Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose/ Suspension)	**1 mg/kg/day (LOEL):** ↓ WBC, ↓ lymphocytes, ↓ eosinophils, ↓ basophils, ↓ large unstained cells, ↓ RBC count, ↓ HCT, ↓ HGB, ↑ neutrophils (F), ↓ spleen weight, ↓ T lymphocytes, T-cells (CD3+), T-cell subtypes (CD4+, CD8+), B cells (CD45RA+), NK cells (CD161+). **10 mg/kg/day:** Same as above, + ↓ reticulocytes; neutrophils, ↑ glucose, ↑ alkaline phosphatase; ↓ triglycerides (F), ↓ spleen weight, lymphoid atrophy (lymph nodes, spleen, thymus) (F), alveolar histiocytosis. **100 mg/kg/day:** Same as above, + ↑ neutrophils, ↑ reticulocytes, ↑ globulin; ↓ triglycerides, ↑ liver weight; ↓ thymus weight, lymphoid atrophy (GALT), hepatocellular hypertrophy.
1-Month Oral Toxicity Study with 1-Month Recovery in Cynomolgus Monkeys (01-2063-09)	4 Weeks	Monkey/ Cynomolgus	3/sex/dose	10, 50, 100 Oral gavage, TID[d], 5 mL/kg, 0.5% Methylcellulose/ Suspension	**10 mg/kg/day:** ↓ lymphocytes, ↓ lymphocyte subsets (helper T cells, cytotoxic/suppressor T cells, and NK cells, ↓ HGB. **50 mg/kg/day:** Same as above, + death, body weight loss, decreased activity, ↑ WBC, ↓ RBC count, ↓ HCT, ↓ reticulocytes, ↑ AST, ↑ ALT, ↓ Ca, ↓ neutrophil pool, slight granulocytic depletion in bone marrow, lymphoid depletion in spleen, bacterial and viral infection secondary to immunosuppression in heart, kidney, gastrointestinal tract, buccal cavity, and skin. **100 mg/kg/day:** Same as above (except no ↑ WBC count), + RBC depletion in bone marrow, and ↑ immature myeloid cells in bone marrow, lymphoid depletion in mesenteric lymph node. **50 mg/kg/day (Recovery:** Complete recovery with the exceptions of partial recovery of ↑ neutrophils, ↑ ALT and ↑ AST, ↓ (CD16+, CD3-), ↓ RBC

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
					count; rebound effect in lymphocytes, (CD4+, CD3+), and (CD8+, CD3+), lymphocytes, and reticulocytes.
39-Week Oral Toxicity Study in Monkeys (2003-0301)	39 weeks	Monkey/ Cynomolgus	4/sex/dose	0.5, 2, 10[e] Oral gavage, BID, 10 mL/kg, 0.5% Methylcellulose/ Suspension	**0.5 mg/kg/day (LOEL):** ↓ total lymphocytes, ↓ lymphocyte subsets (T-helper, -cytotoxic/suppressor and NK cells); lymphoid hyperplasia (2/4 M). **2 mg/kg/day:** Same as above +, ↓ RBC count, ↓ HCT, ↓ HGB, lymphoid hyperplasia (4/4 M) **10 mg/kg/day:** Same as above, + death,↑ reticulocytes; RBC hyperplasia in bone marrow; lymphoid hyperplasia (3/4 M, 1/4 F); lymphoma (1/4 M, 2/4 F; 2 confirmed B-cell origin), mononuclear cell infiltrates in the heart (F).
Genotoxicity					
In Vitro Studies					
Microbial Reverse Bacterial Mutation Assay (AMES) (01-2063-11)	In Vitro	*Salmonella typhimurium, Escherichia coli*	NA	0.010-5 mg/plate Plate Incorporation for ~ 48 to 72 hours at 37°C	No genotoxic effect. No cytotoxic effect.
Mammalian Cell Mutation Assays (01-2063-16)	In Vitro	Chinese Hamster ovary (CHO)-K1-BH4 cells,	NA	16-5000 µg/mL 5-hour treatment, 6-8 day incubation	- No Genotoxic effects - Substantial cytotoxicity at 950, 1000, and 1100 µg/mL with average Day 3 relative cell survivals of 43%, 29%, and 17%, respectively.
In Vitro Cytogenetics Assay (01-2063-10)	In Vitro	Human Peripheral Lymphocytes	NA	41.8-2400 µg/mL 3 hours with activation, 3 and 24 hours without activation	**Cytotoxic Effects:** ~ 50% Mitotic suppression achieved in all treatments. **Genotoxic Effects:** tofacitinib did not significantly increase structural chromosome aberrations at 3- and 24-hour treatments without metabolic activation. At 3 hours with metabolic activation, tofacitinib increased structural chromosome aberrations at relatively cytotoxic concentrations.

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
In Vivo Studies					
In Vivo/In Vitro Rat Hepatocyte Unscheduled DNA Synthesis Study (01-2063-17)	Single Dose Hepatocytes, 2-4 and 14-16 HPD	Rat/Sprague-Dawley	M	125, 250, 250 Oral gavage, 10 mL/kg, 0.5% Methylcellulose	**Toxic/Cytotoxic Effects:** Hypoactivity, labored breathing and/or squinted eyes in the 500 mg/kg group **Genotoxic Effects:** None
In Vivo Cytogenetics (Rat Micronucleus) (01-2063-12)	Once daily for 3 days	Rat/Sprague-Dawley	6M, 6F	62.5, 125, 250 Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose	**Toxic/Cytotoxic Effects:** No mortality or adverse clinical signs attributed to drug treatment was observed. A statistically significant decrease in mean percent body weight gain was evident in the male rats. The males also showed statistically significant treatment-related reduction in mean %PCE, suggestive of bone marrow toxicity. **Genotoxic Effects**: None.
Carcinogenicity					
6-Month Oral Gavage Study in Mice (8200-368)	6 Months	Mouse/Model 001178-T (hemizygous), CB6F1/Jic-TgrasH2@Tac Mouse/Model 001178-W (homozygous wild-type), CB6F1/Jic-TgrasH2@Tac	25/sex/dose	25, 75, 200 Oral gavage, QD, 10 mL/kg, 0.5% (w/v) Methylcellulose/ Solution	**≥25 mg/kg/day:** No evidence of treatment-related carcinogenicity.
2-Year Oral Gavage in Rats (6348-463)	103 Weeks[f]	Rat/Sprague-Dawley	60-70/ sex/dose	10/10, 30/30, 75/100[g] Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose/ Solution	**10 mg/kg/day:** Benign angiomas of mesenteric lymph nodes (M). **30 mg/kg/day:** Hyperplasia and benign tumors of interstitial cells of testes (M), malignant hibernomas of multiple organs (F). **75 mg/kg/day:** Same as above (M). **100/75 mg/kg/day**: Benign thymoma in thymus (F).
Investigative					
14-Day Oral Investigative Study in Rats (10GR431)	14 Days	Rat/Sprague-Dawley	8F with BrdU pumps 5F without BrdU pumps	Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose/ Solution	Tofacitinib inhibited JAK/STAT signaling in BAT as evidenced by decreased tissue levels of

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
					phosphorylated STAT3 (pSTAT3) and pSTAT5 at doses ≥10 mg/kg/day.
Investigative Study with Rat Brown Adipocytes (11GR016)	1 hour pre-incubation with XELJANZ then 20 minutes with oPRL and XELJANZ	Rat/Sprague-Dawley/Primary Leydig cells	In vitro	150 mM NaCl, 0.03 mM $NaHCO_3$ /Solution (oPRL), 0.1% dimethyl sulphoxide/Solution (XELJANZ)	Tofacitinib inhibited the prolactin-induced increase in STAT5A/B phosphorylation.
Investigative Study with Rat Primary Leydig Cells (11GR015)	1 hour pre-incubation with XELJANZ then 15 minutes with oPRL and XELJANZ	Rat/Sprague-Dawley/ Differentiated primary brown adipocytes/ pSTAT5A/B protein	In vitro	150 mM NaCl, 0.03 mM $NaHCO_3$ /Solution (oPRL), 0.1% dimethyl sulphoxide/Solution (XELJANZ)	Tofacitinib inhibited the prolactin-induced increase in STAT5A/B phosphorylation.
Reproductive and Developmental Toxicity					
Oral Fertility and Embryonic Development Study in Male and Female Rats (05GR051)	**(F) Phase 1**: 14 Days premating, throughout cohabitation and through GD 7. **(M) Phase 2**: Minimum of 63 days (beginning 28 days premating)	Rat/Sprague Dawley	20/sex/dose	1, 10, 100 Oral Gavage, QD, 10 mL/kg	**1 mg/kg/day**: No effect. **10 mg/kg/day**: ↑ Postimplantation loss. **100 mg/kg/day**: Same as above, + ↓ pregnancy rate, ↓ corpora lutea, ↓ implantation sites, ↓ viable fetuses, ↑ early resorptions, ↑ pre-implantation loss.
Oral Embryo-Fetal Development Study in Rats (04-2063-24)	GD 6-17	Rat/Sprague Dawley	20F/dose	1, 10, 30 Oral gavage, QD, 10 mL/kg	**≥1 mg/kg/day:** No effect.
Oral Embryo-Fetal Development Study in Rats (09GR353)	GD 6-17	Rat/Sprague Dawley	20F/dose	30, 100, 300 Oral gavage, QD, 10 mL/kg	**30 mg/kg/day:** No effect. **100 mg/kg/day:** ↓ Viable fetuses, ↓ uterine weight, external, visceral and skeletal malformations.

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
					300 mg/kg/day: ↓ Maternal body weight and food consumption, clinical signs of poor toleration, no viable fetuses to examine.
Oral Embryo-Fetal Development Study in Rabbits (05-2063-25)	GD 7-19	Rabbit/New Zealand White	20F/dose	10, 30, 100 Oral gavage, QD, 2 mL/kg	**10 mg/kg/day:** No effect. **30 mg/kg/day:** ↓ Viable fetuses, ↓ uterine weight, external, visceral, and skeletal malformations. **100 mg/kg/day:** Same as above, + ↓ fetal body weights, ↑ visceral variations.
Oral Developmental Peri/Postnatal Reproduction including Postnatal Behavioral/Functional Evaluation in Rats (LIA00468)	GD 6 - DL 21 (or GD 24 for rats not delivering a litter)	Rat/Sprague-Dawley	25F/dose	Oral gavage, QD during dosage period; 10 mL/kg	**10 mg/kg/day**: No effect **50 mg/kg/da**y: ↓ Delivered pups, ↓ liveborn pups, ↓ pup survival, ↓ pup body weight.
Developmental and Reproductive - Juvenile					
Oral Fertility Study in Juvenile Rats (10GR250)	PND 21-70 (M) PND 21-55 (F)	Rat/Sprague-Dawley	20/sex/dose	1, 10, 100 Oral gavage, QD, 10 mL/kg 0.5% (w/v) Methylcellulose/ Suspension	**1 mg/kg/day:** No effect. **10 mg/kg/day:** ↓ BW (M), ↓ BW gain (M). **100 mg/kg/day:** Same as above (M&F).
Oral Toxicity Study in Juvenile Rats with a 2-Month Recovery (10GR307)	PND 21-49	Rat/Sprague Dawley	16/sex/dose	1, 10, 100 Oral gavage, QD, 10 mL/kg 0.5% (w/v) Methylcellulose/ Suspension	**1 mg/kg/day:** Females: ↓WBC, ↓ lymphocytes, eosinophils, basophils Males only: ↑ vacuolation in brown adipose tissue, ↓ T cells, ↓ helper T cells, ↓ cytotoxic T cells, ↓ B cells, ↓ NK cells. **10 mg/kg/day:** Same as above, ↓ T cells, ↓ helper T cells, ↓cytotoxic T cells, ↓B cells, ↓ NK cells. Males: ↓ WBC, ↓ lymphocytes, eosinophils, basophils. Females: ↓ body weight and body weight gain, ↓ reticulocytes, ↓ cellularity (thymus) - females, ↓ cellularity (spleen), ↓ lymphoid cellularity-mesenteric lymph node.

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
					100 mg/kg/day: Same as above, ↓ body weight and body weight gain (M), ↓ RBC, ↓ cellularity: inguino-femoral lymph node, mandibular lymph node.
39-Week Oral Toxicity in Juvenile Monkeys with a 26-Week Recovery (Interim Report) (2501-010)	39 Weeks	Monkey/ Cynomolgus	4/sex/dose	0.5, 2, 10 Oral gavage, BID, 5 mL/kg 0.5% (w/v) Methylcellulose/ Suspension	**0.5 mg/kg/day:** No effect. **2 mg/kg/day:** ↓ total lymphocytes (M), ↓ lymphocyte subsets (NK cells, effector CD8+ T cells, CD8+ T cells (M), ↓ thymus weight (M), ↓ spleen weight (F). **10 mg/kg/day:** ↓ total lymphocytes (M + F), ↓ RBC count, ↓ HCT, ↓ HGB, ↓ lymphocyte subsets (NK cells, CD4+ and CD8+ T cells, naïve CD4+ and CD8+ T cells, central and effector memory CD8+ cells), ↓ spleen and thymus weight.

[a] Doses are expressed as mg active moiety/kg/day unless otherwise noted.
[b] Five/sex were necropsied on Day 2 and 5/sex were retained for a 14-day recovery period and necropsied on Day 15.
[c] 13, 67, 333 mg/kg TID; 7 hours apart.
[d] 3.33, 16.7, 33.3mg/kg TID; 7 hours apart.
[e] 0.25, 1, 5, mg/kg BID; 12 hours apart.
[f] All surviving males in Group 4 were sacrificed on Day 654 (Week 94) of the dosing phase. All surviving males in Group 1 through Group 3 were sacrificed on Day 686 (Week 98) of the dosing phase. All surviving females were sacrificed on Day 715 (Week 103) of the dosing phase.
[g] Dose was lowered from 100 to 75 mg/kg/day starting on Day 133.
ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BAT = Brown adipose tissue; BID = Twice daily; BrdU = 5-bromo-2'deoxyuridine; BUN = Blood urea nitrogen; Ca = Calcium; CHO = Chinese hamster ovary; CD = Cluster of differentiation; DL = Day of lactation; F = Female; GALT = Gut associated lymphoid tissue; GGT = Gamma glutamyl transferase; GD = Gestation Day; HGB = Hemoglobin; HCT = Hematocrit; HPD = Hours postdose; IV = Intravenous; JAK = Janus kinase; LOEL = Lowest observed effect level; M = Male; NA = Not applicable; NaCl = Sodium chloride; $NaHCO_3$ = Sodium bicarbonate; NK = Natural killer; oPRL = Ovine prolactin; PND = Postnatal day; PCE = Polychromatic erythrocytes; pSTAT = Phosphorylated signal transducer and activator of transcription; QD = Once daily; RBC = Red blood cells; STAT = Signal transducer and activator of transcription; TID = Three times daily; WBC = White blood cells.

REFERENCES

1. Fleischmann R et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum 2012 64:(3) 624-629.

2. Ghoreschi K, Jesson MI, Li X, et al. Modulation of Innate and Adaptive Immune Responses by Tofacitinib (CP-690,550). J Immunol 2011;186(7):4234-43.

3. Gupta P J. A semi-mechanistic model of CP-690,550-induced reduction in neutrophil counts in patients with rheumatoid arthritis. Clin Pharmacol. 2010 Jun; 50(6):679-87. Epub 2009 Oct 30.

4. Karaman MW, Herrgard S, Treiber DK, et al. A quantitative analysis of kinase inhibitor selectivity. Nat Biotechnol 2008;26:127-32.

5. Kremer JM et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum 2009 60:(7): 1895-1905.

6. Kremer JM et al. A Phase 2B dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and inadequate response to methotrexate alone. Arthritis Rheum 2011Oct e-pub.
7. Meyer DM, Jesson MI. Anti-inflammatory activity and neutrophil reductions mediated by the JAK1/JAK3 inhibitor, CP-690,550, in rat adjuvant-induced arthritis. J Inflamm (Lond) 2010;7:41.

8. Russell S, Tayebi N, Nakajima H, et al. Mutation of JAK3 in a patient with SCID: essential role of JAK3 in lymphoid development. Science 1995;270:797-800.

9. Thomis D, Berg L. The role of JAK3 in lymphoid development, activation, and signaling. Curr Opin Immunol 1997;9:541-7.

10. Walker J, Smith M. The JAK/STAT Pathway in Rheumatoid Arthritis. J Rheum 2005; 32(9):1650-3.

11. Van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367:508-19.

PART III: CONSUMER INFORMATION

PrXELJANZ®
Tofacitinib tablets

Pr XELJANZ® XR
Tofacitinib extended-release tablets

This leaflet is part III of a three-part "Product Monograph" published when XELJANZ/XELJANZ XR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about XELJANZ/XELJANZ XR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Rheumatoid Arthritis
XELJANZ/XELJANZ XR (tofacitinib) is used to treat rheumatoid arthritis (RA) when other treatments do not work.

Psoriatic Arthritis
XELJANZ is used to treat active psoriatic arthritis (PsA) when other medicines do not work.

Ulcerative Colitis
XELJANZ is used to treat moderately to severely active ulcerative colitis (UC) when other medicines do not work

What it does:
XELJANZ/XELJANZ XR is believed to interfere with the activity of an enzyme called Janus kinase (JAK), which activates other cellular components which normally start the immune response in your body. By reducing the immune response XELJANZ/XELJANZ XR reduces the signs and symptoms of rheumatoid arthritis and psoriatic arthritis. XELJANZ also reduces the sign and symptoms of ulcerative colitis.

When it should not be used:
- If you are allergic to tofacitinib or any other non-medicinal ingredients in XELJANZ/XELJANZ XR, you should not take XELJANZ/XELJANZ XR (see **What the non-medicinal ingredients are**).
- Do not take this medication if you are pregnant or are planning to become pregnant.
- Do not take this medication if you are breast-feeding or intend to breast-feed. Talk to your doctor about how to feed your child while taking XELJANZ/XELJANZ XR.
- Do not take this medication if you have a severe liver insufficiency.

What the medicinal ingredient is:
The active ingredient of XELJANZ/XELJANZ XR is called tofacitinib citrate

What the non-medicinal ingredients are:
XELJANZ:
The 5 mg tablet core contains: Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. The film coat contains HPMC 2910/Hypromellose 6 cP, Lactose Monohydrate, Macrogol/PEG 3350, Titanium dioxide, Triacetin (Glycerol Triacetate)

The 10 mg tablet core contains: Microcrystalline Cellulose, Lactose Monohydrate, croscarmellose Sodium, Magnesium Stearate. The film coat contains: HPMC 2910/Hypromellose 6cP, titanium dioxide, lactose monohydrate, macrogol/PEG3350, triacetin (glycerol triacetate), FD&C blue #2/indigo carmine aluminum lake, FD&C blue #1/brilliant blue FCF aluminum lake.

XELJANZ XR: ammonium hydroxide, cellulose acetate, copovidone, ferrosoferric oxide/black iron oxide, hydroxyethyl cellulose, hydroxypropyl cellulose, HPMC 2910/hypromellose, magnesium stearate, propylene glycol, red iron oxide, shellac glaze, sorbitol, titanium dioxide, triacetin.

What dosage forms it comes in:
XELJANZ is supplied as 5 mg and 10 mg tablets and is available in bottles or foil blisters.

XELJANZ XR is supplied as 11 mg tablets and is available in bottles.

WARNINGS AND PRECAUTIONS

Serious Warning and Precautions

- XELJANZ/XELJANZ XR is a medicine that affects your immune system and can lower the ability of your body to fight infections such as tuberculosis, and infections caused by other bacteria, fungi, or viruses that can spread throughout the body. These infections may lead to hospitalization or death. Most patients who developed these infections were taking other medicines that make it harder to fight infections at the same time such as methotrexate or corticosteroids. You should not be using XELJANZ/ XELJANZ XR if you have any kind of infection.
- If a serious infection develops, stop XELJANZ/XELJANZ XR and contact your doctor.
- Your doctor will closely monitor you for the signs and symptoms of infection during and after the treatment with XELJANZ/ XELJANZ XR.
- Lymphoma, other cancers and other serious conditions have been reported in patients treated with XELJANZ

Blood Clots
- Blood clots in the veins of your legs or arms (deep vein thrombosis, DVT), arteries (arterial thrombosis) or lungs (pulmonary embolism, PE) can happen in some people taking XELJANZ. This may be life-threatening and cause death.

- If you develop any signs or symptoms of a blood clot in your leg (such as swelling, pain or tenderness in the leg) or in your lung (such as sudden unexplained chest pain or shortness of breath) stop XELJANZ and seek immediate medical help.

BEFORE or while taking XELJANZ or XELJANZ XR, tell your healthcare professional if you:

- think you have an infection or have symptoms of an infection such as:
    - fever, sweating, or chills,
    - muscle aches,
    - cough,
    - shortness of breath,
    - blood in spit,
    - weight loss,
    - warm, red, or painful skin or sores on your body,
    - diarrhea or stomach pain,
    - burning when you urinate or urinating more often than normal,
    - feeling very tired;
- are being treated for an infection, get a lot of infections or have infections that keep coming back;
- have diabetes, HIV/AIDS, or a weak immune system. People with these conditions have a higher chance for infections;
- have tuberculosis, or a history of tuberculosis or have been in close contact with someone with tuberculosis;
- have or have had hepatitis B or C;
- have gastrointestinal perforations (tear in the stomach or intestines);
- have diverticulitis (inflammation in parts of the large intestine);
- have ulcers in your stomach or intestines;
- have low blood counts: treatment with XELJANZ/XELJANZ XR can be associated with low red blood cell counts (anemia), or with low white blood cell counts (neutrophils or lymphocytes). Your healthcare professional will monitor your blood counts regularly after you start XELJANZ/XELJANZ XR, and may adjust your dose of XELJANZ/XELJANZ XR or withhold the drug temporarily in the event your blood counts drops too low, or administer additional supportive medicines to help your body regain normal blood cell levels;
- have high cholesterol. Your healthcare professional should monitor your liver tests and blood cholesterol levels 4-8 weeks after you start receiving XELJANZ/XELJANZ XR and routinely thereafter;
- have or had any type of cancer;
- have liver or kidney problems;
- have a history of interstitial lung disease;
- have muscle pain or muscle weakness;
- develop new skin lesions during or after therapy or if existing lesions change appearance;
- are planning to get vaccinated. Certain types of vaccines (shots) should not be given when taking XELJANZ/XELJANZ XR. Before you start XELJANZ/XELJANZ XR, you should be up to date with all recommended vaccinations, including a shingles vaccine;
- have chest pain or any heart problems;
- are over the age of 65 or of Asian descent, you may be at increased risk of serious side effects.
- have had blood clots in your legs (deep vein thrombosis) or lungs (pulmonary embolism) or have been told you are at risk of blood clots. Blood clots in the legs and lungs can happen in some people taking XELJANZ. This may be life-threatening and cause death. If you have any signs or symptoms of blood clots while you are being treated with XELJANZ, including swelling, pain or tenderness in the leg, sudden unexplained chest pain, or shortness of breath, stop XELJANZ and seek immediate medical help.
- have problems with your blood clotting (thrombophilia)
- have chest pain
- have heart failure or any heart problems

BEFORE or while taking XELJANZ XR, tell your doctor if you have known narrowing or blockage of your digestive tract (intestines or another part of your bowel are not as wide as normal).

If you are of child-bearing age, you should use an effective method of birth control while taking XELJANZ/XELJANZ XR and for 4 to 6 weeks after you stop taking XELJANZ/XELJANZ XR.

INTERACTIONS WITH THIS MEDICATION

It is important that your healthcare professional be aware of all medications you are taking prior to starting XELJANZ/XELJANZ XR including biologics such as Cimzia™, Cosentyx®, Enbrel®,Humira®, Kineret®, Orencia®, Remicade®, Rituxan®, Entyvio®, Simponi™ and Stelara®.

- Tell your doctor if you are taking immunosuppressants (e.g. azathioprine, 6-mercaptopurine, tacrolimus, sirolimus, cyclosporine), antiarrythmics, beta-blockers, calcium channel blockers, cholinesterase inhibitors, HIV protease inhibitors, rifampin, ketoconazole, fluconazole.
- Tell your doctor if you have received any vaccines (shots) within 1 month prior to starting XELJANZ /XELJANZ XR.
- Avoid grapefruit juice.
- St. John's Wort (an herbal medicine also known as hypericum perforatum) may reduce the response to XELJANZ/XELJANZ XR.

PROPER USE OF THIS MEDICATION

XELJANZ/XELJANZ XR can be taken with or without food.

Your doctor may reduce the dose if you have liver or kidney problems. You should not increase the dose.

XELJANZ/XELJANZ XR should not be used if you have or develop a serious infection until the infection is controlled.

Usual adult dose:

Rheumatoid Arthritis:
- The recommended dose of XELJANZ is 5 mg taken by mouth twice daily.
- The recommended dose of XELJANZ XR is 11 mg taken by mouth once daily. Swallow XELJANZ XR tablets whole. Do not crush, split or chew the tablets.
- Patients taking XELJANZ/XELJANZ XR are usually also prescribed methotrexate.

Psoriatic Arthritis:
- The recommended dose of XELJANZ is 5 mg taken by mouth twice daily.
- Patients taking XELJANZ are also prescribed methotrexate or another conventional synthetic DMARD (csDMARD).

Ulcerative Colitis:
- The recommended dose of XELJANZ is 10 mg twice daily for the first 8 weeks. After 8 weeks, your doctor will decide to give you 5 mg or 10 mg twice daily for maintenance.
- Your doctor may decide to stop XELJANZ if XELJANZ does not work for you within 16 weeks.
- XELJANZ may be used together with certain other medicines, such as corticosteroids and aminosalicylates to treat ulcerative colitis.

Overdose

In case of a drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you have missed your dose of XELJANZ/XELJANZ XR, take the next dose as planned at the next scheduled time. Do not take a double dose to make up for a forgotten dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

These are not all the possible side effects you may feel when taking XELJANZ/XELJANZ XR. If you experience any side effects not listed here, contact your healthcare professional.

The side effects of XELJANZ/XELJANZ XR include:

- Upper respiratory tract infection (such as a cold)
- Nasopharyngitis (nose or throat infection runny or stuffy nose)
- Headache
- Diarrhea
- Nausea (feeling queasy, feeling like you may throw up)
- Indigestion (heartburn or upset stomach)
- Cough
- Dizziness
- Vomiting
- Back pain
- Joint pain
- Rash
- Muscle weakness/pain

If any of the above affects you severely, tell your doctor or pharmacist.

XELJANZ/XELJANZ XR may cause abnormal blood test results, including changes in cholesterol levels, white or red blood cell counts or creatinine levels (a protein that may increase in people with kidney problems). Your doctor will decide when to perform blood tests and will interpret the results.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Pneumonia: infection with coughing, fever, fatigue		✓	
Urinary tract infections: difficulty or increased need to urinate, pain or burning sensation when passing urine, pain in the pelvis or mid-back, urine that appears cloudy		✓	
High blood pressure		✓	
Gastritis: abdominal pain, loss of appetite		✓	
Shingles/Herpes Zoster: skin rash or blisters usually on one side of the body with itching, burning or tingling pain			✓
Cellulitis: skin infection with redness, swelling and painful skin		✓	
UNCOMMON			
Blood clot in the leg (deep vein thrombosis): swelling, pain or tenderness in the leg			✓
Blood clot in the lung (pulmonary embolism): chest pain, or shortness of breath			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Bronchitis: persistent cough, fatigue, shortness of breath		✓	
Flu: cough, sore throat, feverish chills		✓	
Skin cancer: lesions during or after therapy or if existing lesions change appearance		✓	
Increased creatine kinase levels: muscle weakness and/or muscle pain	✓		
Kidney problems: change in the amount, frequency or colour (pale or dark) of urine		✓	
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, throwing up, loss of appetite with itching			✓
Low blood cell counts (anemia/neutropenia/ lymphopenia): fatigue, loss of energy, weakness, shortness of breath		✓	
Peripheral edema: swelling of legs and ankles or the arms and hands		✓	
Congestive heart failure: shortness of breath when you exert yourself or lie down, swelling in your legs, ankles and feet, irregular heartbeat, persistent cough			✓

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect	**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Allergic reaction: hives, rash, swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

HOW TO STORE IT

Store between 15°C and 30°C.
Keep out of sight and reach of children.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about XELJANZ/ XELJANZ XR:

- Talk to your healthcare professional;
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Website (https://www.canada.ca/en/health-canada.html), the manufacturer's website (http://www.Pfizer.ca) or by calling the sponsor, Pfizer Canada ULC, at 1-800-463-6001.

This leaflet was prepared by Pfizer Canada ULC

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