▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

XELJANZ® tofacitinib (as citrate)

1 NAME OF THE MEDICINE

XELJANZ tofacitinib (as citrate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Tofacitinib citrate is a white to off-white powder with a pKa of 5.07. Tofacitinib citrate is freely soluble in N,N-Dimethylacetamide, slightly soluble in water, and very slightly soluble in ethanol (99.5% ethanol). The partition coefficient is 14.3 (Log P=1.15).

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

Excipients with known effect
Contains sugars (lactose monohydrate).

XELJANZ 10 mg film-coated tablet

Each 10 mg tablet contains 16.155 mg of tofacitinib citrate equivalent to 10 mg of tofacitinib free base active pharmaceutical ingredient.

Excipients with known effect
Contains sugars (lactose monohydrate).

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

3 PHARMACEUTICAL FORM

Film-coated tablet.

XELJANZ 5 mg
White, round, immediate release, tablet debossed with “Pfizer” on one side, and “JKI 5” on the other side.

XELJANZ 10 mg

Blue, round, immediate release, tablet debossed with “Pfizer” on one side, and “JKI 10” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rheumatoid Arthritis

XELJANZ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. XELJANZ can be used alone or in combination with conventional synthetic disease-modifying antirheumatic drugs (DMARDs), including methotrexate.

Psoriatic Arthritis

XELJANZ in combination with conventional synthetic DMARDs is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response to a prior DMARD therapy.

Ulcerative Colitis

XELJANZ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.

4.2 Dose and Method of Administration

Therapy with XELJANZ should be initiated and monitored by a specialist physician with expertise in the management of conditions for which XELJANZ is indicated (e.g. rheumatologist or gastroenterologist).

Important Administration Instructions

- Do not initiate XELJANZ in patients with an absolute lymphocyte count (ALC) less than 0.75 x 10^9 cells/L, an absolute neutrophil count (ANC) less than 1x 10^9 cells/L or who have haemoglobin levels less than 90 g/L.
- Dose adjustment or interruption is recommended for management of lymphopenia, neutropenia, and anaemia (see Section 4.4 Special Warnings and Precautions For Use)
- Interrupt use of XELJANZ if a patient develops a serious infection until the infection is controlled.
- Take XELJANZ with or without food.

Method of Administration

Recommended Dosage in Rheumatoid Arthritis and Psoriatic Arthritis

Table 1 displays the recommended adult daily dosage of XELJANZ for rheumatoid arthritis and psoriatic arthritis, and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, in patients with renal or hepatic impairment, with lymphopenia, neutropenia, or anaemia.

Table 1: Recommended Dosage of XELJANZ in Patients with Rheumatoid Arthritis[1] and Psoriatic Arthritis[2]	
	XELJANZ
Adult patients	5 mg twice daily
Interactions with Other Medicines[3]	
Patients receiving: · Potent CYP3A4 inhibitors (e.g., ketoconazole), or · a moderate CYP3A4 inhibitor(s) with a potent CYP2C19 inhibitor(s) (e.g., fluconazole) (see Section 4.5 Interactions With Other Medicines and Other Forms of Interactions).	5 mg once daily
Renal Impairment[4]	
Patients with estimated GFR less than or equal to 50 mL/min (including but not limited to those with severe renal impairment who are undergoing haemodialysis) (see Section 4.4 Special Warnings and Precautions For Use and Section 5.2 Pharmacokinetic Properties).	5 mg once daily
Hepatic Impairment[5]	
Patients with moderate hepatic impairment (see Section 4.4 Special Warnings and Precautions For Use and Section 5.2 Pharmacokinetic Properties).	5 mg once daily
Lymphopenia	
Patients with ALC $\geq 0.75 \times 10^9$ cells/L.	Maintain dose
Patients with persistent decrease (2 sequential values on routine testing) in ALC in the range of $0.5 - <0.75 \times 10^9$ cells/L.	Interrupt dosing. When ALC is $\geq 0.75 \times 10^9$ cells/L, resume 5 mg twice daily.
Patients with ALC $<0.5 \times 10^9$ cells/L (lab value confirmed by repeat testing within 7 days).	Discontinue dosing
Neutropenia	
Patients with ANC $>1.0 \times 10^9$ cells/L.	Maintain dose
Patients with persistent decrease (2 sequential values on routine testing) in ANC in the range of $0.5 - 1.0 \times 10^9$ cells/L.	Interrupt dosing. When ANC is $>1.0 \times 10^9$ cells/L, resume 5 mg twice daily
Patients with ANC $<0.5 \times 10^9$ cells/L (confirmed by repeat testing).	Discontinue dosing

Anaemia	
Patients with haemoglobin ≤20 g/L decrease and ≥90 g/L.	Maintain dose
Patients with haemoglobin >20 g/L decrease or <80 g/L (confirmed by repeat testing).	Interrupt dosing until haemoglobain values have normalised.

[1] XELJANZ may be used as monotherapy or in combination with methotrexate or other conventional synthetic DMARDs (csDMARDs) in rheumatoid arthritis.
[2] XELJANZ is used in combination with csDMARDs in psoriatic arthritis. The efficacy of XELJANZ as monotherapy has not been studied in patients with psoriatic arthritis.
[3] Coadministration of XELJANZ with potent CYP inducers (e.g., rifampicin) may result in loss of or reduced clinical response (see Section 4.5 Interactions With Other Medicines and Other Forms of Interactions). Coadministration of potent inducers of CYP3A4 with XELJANZ is not recommended.
[4] No dose adjustment is required in patients with estimated GFR more than 50 mL/min.
[5] No dose adjustment required in patients with mild hepatic impairment. XELJANZ should not be used in patients with severe hepatic impairment (see Section 4.3 Contraindications and Section 5.2 Pharmacokinetic Properties).

Recommended Dosage in Ulcerative Colitis

Table 2 displays the recommended adult daily dosage of XELJANZ for ulcerative colitis, and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, in patients with renal or hepatic impairment, with lymphopenia, neutropenia, or anaemia.

Table 2: Recommended Dosage of XELJANZ in Patients with Ulcerative Colitis	
	XELJANZ
Adult patients	The recommended dose for adult patients with moderately to severely active ulcerative colitis is 10 mg twice daily for induction for 8 weeks and 5 mg twice daily for maintenance. For patients who do not achieve adequate therapeutic benefit by week 8 (e.g. those with the greatest disease activity or those refractory to tumour necrosis factor (TNF)-inhibitors), the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. Continued treatment is not recommended for patients who have not shown a clinical response by Week 16 (see Section 5.1 Clinical Trials, Ulcerative Colitis). Use the lowest effective dose to maintain response. Following end of induction therapy, the choice of maintenance therapy should be based on individual consideration of the patient's

	clinical response and treatment history. For refractory patients, such as those who have failed prior TNF inhibitor therapy, consideration may be given to continuation of the 10 mg twice daily dose for maintenance in order to maintain therapeutic benefit. Patients who fail to maintain therapeutic benefit on XELJANZ 5 mg twice daily may benefit from an increase to XELJANZ 10 mg administered twice daily for maintenance. In patients who have responded to treatment with XEJLANZ, corticosteroids may be reduced and/or discontinued in accordance with standard of care. *Retreatment in UC* If therapy is interrupted, restarting treatment with XELJANZ can be considered. If there has been a loss of response, reinduction with XELJANZ 10 mg twice daily may be considered. The treatment interruption period in clinical studies extended up to 1 year. Efficacy may be regained by 8 weeks of 10 mg twice daily therapy (see Section 5.1 Pharmacodynamic Properties, Clinical trials).
Interactions with Other Medicines[1]	
Patients receiving: · Potent CYP3A4 inhibitors (e.g., ketoconazole), or · a moderate CYP3A4 inhibitor(s) with a potent CYP2C19 inhibitor(s) (e.g., fluconazole) (see Section 4.5 Interactions With Other Medicines and Other Forms of Interactions).	If taking 10 mg twice daily, reduce to 5 mg twice daily If taking 5 mg twice daily, reduce to 5 mg once daily
Renal Impairment[2]	
Patients with estimated GFR less than or equal to 50 mL/min (including but not limited to those with severe renal impairment who are undergoing haemodialysis), the recommended dose is half the total daily dose indicated for patients with normal renal function (see Section 4.4 Special	If taking 10 mg twice daily, reduce to 5 mg twice daily If taking 5 mg twice daily, reduce to 5 mg once daily

Warnings and Precautions For Use and Section 5.2 Pharmacokinetic Properties).	
Hepatic Impairment[3]	
Patients with moderate hepatic impairment, the recommended dose is half the total daily dose indicated for patients with normal hepatic function (see Section 4.4 Special Warnings and Precautions For Use and Section 5.2 Pharmacokinetic Properties).	If taking 10 mg twice daily, reduce to 5 mg twice daily If taking 5 mg twice daily, reduce to 5 mg once daily
Lymphopenia	
Patients with ALC $\geq 0.75 \times 10^9$ cells/L.	Maintain dose
Patients with persistent decrease (2 sequential values on routine testing) in ALC in the range of $0.5 - <0.75 \times 10^9$ cells/L.	Reduce or interrupt dosing. If taking 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, interrupt dosing. When ALC is $\geq 0.75 \times 10^9$ cells/L, resume XELJANZ treatment as clinically appropriate.
Patients with ALC $<0.5 \times 10^9$ cells/L (lab value confirmed by repeat testing within 7 days).	Discontinue dosing
Neutropenia	
Patients with ANC $>1.0 \times 10^9$ cells/L.	Maintain dose
Patients with persistent decrease (2 sequential values on routine testing) in ANC in the range of $0.5 - 1.0 \times 10^9$ cells/L.	Reduce or interrupt dosing until ANC $>1.0 \times 10^9$ cells/L. If taking 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, interrupt dosing. When ANC is $>1.0 \times 10^9$ cells/L, resume XELJANZ treatment as clinically appropriate.
Patients with ANC $<0.5 \times 10^9$ cells/L (confirmed by repeat testing).	Discontinue dosing
Anaemia	
Patients with haemoglobin ≤ 20 g/L decrease and ≥ 90 g/L.	Maintain dose
Patients with haemoglobin >20 g/L decrease or <80 g/L (confirmed by repeat testing).	Interrupt dosing until haemoglobain values have normalised.

[1] Coadministration of XELJANZ with potent CYP inducers (e.g., rifampicin) may result in loss of or reduced clinical response (see Section 4.5 Interactions With Other Medicines and Other Forms of Interactions). Coadministration of potent inducers of CYP3A4 with XELJANZ is not recommended.
[2] No dose adjustment is required in patients with estimated GFR more than 50 mL/min.
[3] No dose adjustment required in patients with mild hepatic impairment. XELJANZ should not be used in patients with severe hepatic impairment (see Section 4.3 Contraindications and Section 5.2 Pharmacokinetic Properties).

Dosage Adjustment in the Elderly

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

Children and Adolescents

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

4.3 Contraindications

Hypersensitivity to tofacitinib citrate or to any of the excipients.

XELJANZ must not be used in combination with biological agents or other potent immunosuppressive agents (see Section 4.5 Interactions With Other Medicines and Other Forms of Interactions).

XELJANZ should not be used in patients with severe hepatic impairment.

4.4 Special Warnings and Precautions For Use

Dose-dependent adverse reactions seen in patients treated with XELJANZ 10 mg twice daily, in comparison to 5 mg twice daily include the following: herpes zoster infections, serious infections, and non-melanoma skin cancer (NMSC).

Therapy with XELJANZ should be initiated and monitored by a specialist physician with expertise in the management of conditions for which XELJANZ is indicated (e.g. rheumatologist or gastroenterologist).

The efficacy of XELJANZ as monotherapy has not been studied in patients with psoriatic arthritis (PsA).

Serious Infections

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

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral or other opportunistic pathogens have been reported in rheumatoid arthritis (RA) patients receiving immunomodulatory agents (these include biological DMARDs as well as 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, oesophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infection, BK virus infections and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localised disease, and were often taking concomitant immunomodulating agents such as methotrexate (MTX) or corticosteroids which, in addition to RA may predispose them to infections. Other serious infections, that were not reported in clinical studies, may also occur (e.g., coccidioidomycosis).

In patients with ulcerative colitis, XELJANZ treatment with 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Additionally, opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with XELJANZ 10 mg twice daily.

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

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

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

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

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

Tuberculosis

Patients should be evaluated and tested for latent or active infection prior to administration of XELJANZ and continue to be evaluated while on treatment.

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

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

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy. The need for repeat testing should be considered during therapy if symptoms develop or if re-exposure occurs.

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. In patients treated with XELJANZ, the incidence of herpes zoster appears to be increased in:

- Japanese or Korean patients.
- Patients with an ALC less than 1.0×10^9 cells/L (see Section 4.2 Dose and Method of Administration).
- Patients with long standing RA who have previously received two or more biological DMARDs.
- Patients treated with 10 mg twice daily.

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

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

Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated NMSC or when considering continuing XELJANZ in patients who develop a malignancy.

The possibility exists for XELJANZ to affect host defenses against malignancies.

Lymphomas have been observed in patients treated with XELJANZ. Patients with RA, particularly those with highly active disease, are at a higher risk (up to several-fold) than the general population for the development of lymphoma. The role of XELJANZ, a Janus kinase (JAK) inhibitor, in the development of lymphoma is uncertain.

Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

The role of treatment with XELJANZ on the development and course of malignancies is not known.

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 Section 4.4 Special Warnings and Precautions For Use, Renal Transplant).

Rheumatoid Arthritis

In the controlled phase 3 clinical studies in RA patients, 26 malignancies (excluding NMSC) including 5 lymphomas, were diagnosed in 26 patients receiving XELJANZ/XELJANZ plus DMARD, compared to 0 malignancies (excluding NMSC) in patients in the placebo/placebo plus DMARD group, 2 malignancies in 2 patients in the adalimumab group and 1 in the MTX group. Three thousand eight hundred (3800) patients (3942 patient-years of observation) were treated with XELJANZ for durations up to 2 years while 681 patients (203 patient-years of observation) were treated with placebo for a maximum of 6 months and 204 patients (179 patient-years of observation) were treated with adalimumab for 12 months. The exposure-adjusted incidence rate for malignancies and lymphoma was 0.66 and 0.13 events per 100 patient-years, respectively, in the XELJANZ groups.

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

Psoriatic Arthritis

In 2 controlled Phase 3 clinical trials in patients with active PsA, there were 3 malignancies (excluding NMSC) in 474 patients (298 patient-years of observation) receiving XELJANZ plus csDMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients (52.3 patient-years) in the placebo plus csDMARD group (3 months exposure) and 0 malignancies in 106 patients (91 patient-years) in the adalimumab plus csDMARD group (12 months exposure). No lymphomas were reported. The exposure-adjusted incidence rate for malignancies (excluding NMSC) was 1.95 patients with events and 0 patients with events per 100 patient-years in the XELJANZ groups that received 5 mg twice daily and 10 mg twice daily, respectively.

In the safety population comprised of the 2 controlled Phase 3 clinical trials and the long-term extension trial (783 patients) the rate of malignancies (excluding NMSC) was 0.72 patients with events per 100 patient-years.

Ulcerative Colitis

No malignancies other than NMSC were reported in the 8-week induction and 52-week maintenance study. In the long-term extension study, malignancies (including solid cancers

and lymphomas) were observed more often in patients treated with XELJANZ 10 mg twice daily compared with patients treated with XELJANZ 5 mg twice daily.

Skin Cancer

Melanoma and NMSCs have been reported in patients treated with XELJANZ. The risk of NMSC may be higher in patients treated with XELJANZ 10 mg twice daily than in patients treated with 5 mg twice daily. Regular skin examinations are recommended, particularly for patients with an increased risk for, or a prior history of, skin cancer.

Renal Transplant

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

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

Cardiovascular

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

Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials in RA patients, although the role of JAK inhibition in these events is not known. Events were primarily reported as diverticular perforation, peritonitis, abdominal abscess and appendicitis. In the RA clinical trials, the incidence rate of gastrointestinal perforation across all studies (phase 1, phase 2, phase 3 and long-term extension) for all treatment groups all doses was 0.11 events per 100 patient-years with XELJANZ therapy. RA patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. The relative contribution of these concomitant medications vs. XELJANZ to the development of gastrointestinal perforations is not known. The incidence rate in the PsA clinical trials (Phase 3 and long-term extension) was 0.08 patients with events per 100 patient-years with XELJANZ therapy.

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

reported in patients treated with XELJANZ and was reported in 1 patient treated with placebo.

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

Hypersensitivity

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

Vaccinations

No data are available on the secondary transmission of infection by live vaccines to patients receiving XELJANZ. Live vaccines should not be given concurrently with XELJANZ. It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating XELJANZ therapy. The decision to use live vaccines prior to XELJANZ treatment should take into account the pre-existing immunosuppression in a given patient.

Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular consideration should be given to patients with longstanding RA who have previously received two or more biological DMARDs. The interval between live vaccinations and initiation of XELJANZ therapy should be in accordance with current vaccination guidelines regarding immunomodulatory agents.

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

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

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

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

Retention of immunisation protection with tofacitinib has not been evaluated.

Interstitial Lung Disease

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

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

Asian Patients

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

Use in hepatic impairment

Subjects with moderate hepatic impairment had 65% higher AUC compared with healthy subjects (see Section 5.2 Pharmacokinetic Properties). XELJANZ has not been studied in patients with severe hepatic impairment, or in patients with positive hepatitis B virus or hepatitis C virus serology. No dose adjustment is required in patients with mild hepatic impairment. In patients with moderate hepatic impairment, the recommended dose is half the total daily dose indicated for patients with normal hepatic function (see Section 4.2 Dose and

Method of Administration). XELJANZ should not be used in patients with severe hepatic impairment (see Section 4.3 Contraindications).

Use in renal impairment

No dose adjustment is required in patients with estimated GFR more than 50 mL/min. In patients with estimated GFR less than or equal to 50 mL/min (including but not limited to those with severe renal impairment who are undergoing haemodialysis), the recommended dose is half the total daily dose indicated for patients with normal renal function (see Section 4.2 Dose and Method of Administration and Section 5.2 Pharmacokinetic Properties).

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

Use in the elderly

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

Paediatric use

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

Effects on laboratory tests

Lymphocytes

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 (see Section 5.1 Pharmacodynamic Properties).

Lymphocyte counts less than 0.75×10^9 cells/L were associated with an increased incidence of serious infections. It is not recommended to initiate or continue XELJANZ treatment in patients with a confirmed lymphocyte count less than 0.75×10^9 cells/L. Lymphocytes should be monitored at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts, see Section 4.2 Dose and Method of Administration.

Neutrophils

Treatment with XELJANZ was associated with an increased incidence of neutropenia ($<2.0 \times 10^9$ cells/L) compared to placebo.

Avoid initiation of XELJANZ treatment in patients with a low neutrophil count (i.e., $<1.0 \times 10^9$ cells/L). For patients who develop a persistent absolute neutrophil count (ANC) of $0.5\text{-}1.0 \times 10^9$ cells/L, reduce XELJANZ dose or interrupt XELJANZ dosing until ANC is $>1.0 \times 10^9$ cells/L. In patients who develop a confirmed ANC $<0.5 \times 10^9$ cells/L treatment with XELJANZ is not recommended. Neutrophils should be monitored at baseline and after

4 to 8 weeks of treatment and every 3 months thereafter (see Section 4.2 Dose and Method of Administration and Section 4.8 Adverse Effects (Undesirable Effects)).

Haemoglobin

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

Lipids

Treatment with XELJANZ was associated with dose-dependent increases in lipid parameters such as total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (see Section 4.8 Adverse Effects (Undesirable Effects)). Maximum effects were generally observed within 6 weeks. There were no clinically relevant changes in LDL/HDL cholesterol ratios. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been established. Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of XELJANZ therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia. Increases in total and LDL cholesterol associated with XELJANZ may be decreased to pretreatment levels with statin therapy.

Liver Enzyme Elevations

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

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

4.5 Interactions With Other Medicines and Other Forms of Interactions

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

Potential for Other Medicines to Influence the Pharmacokinetics of Tofacitinib

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

Methotrexate

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

Ketoconazole

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

Fluconazole

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

Cyclosporin

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

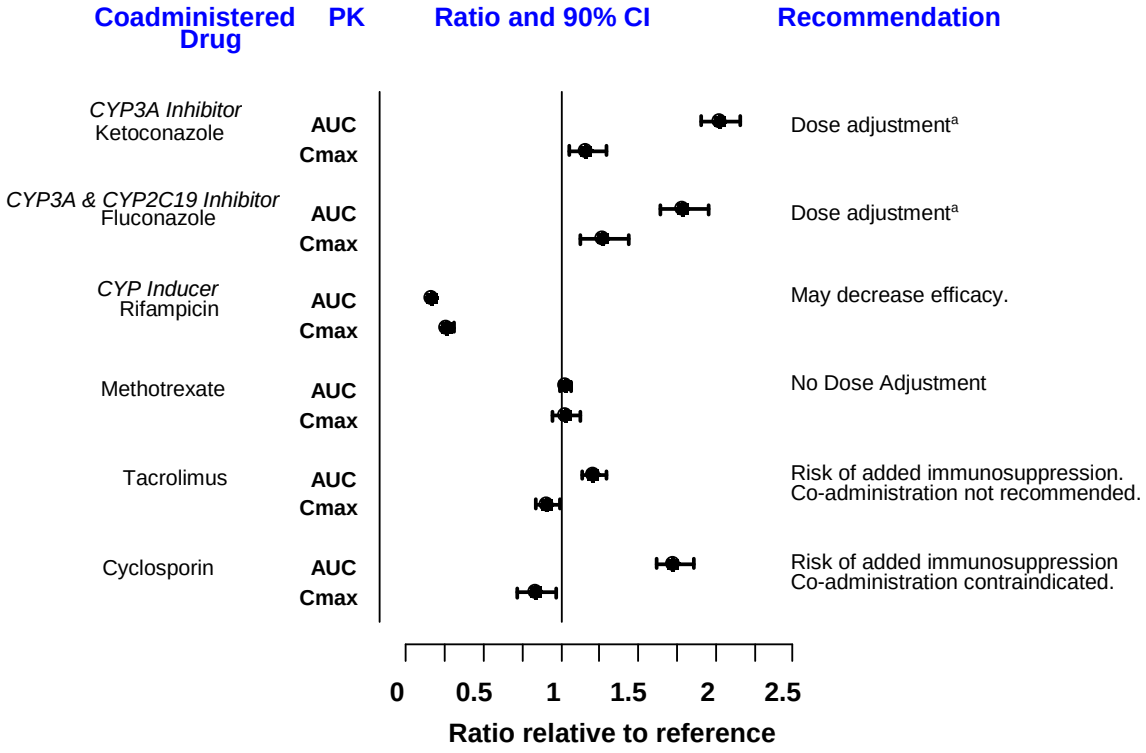
Tacrolimus

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

Rifampicin

Coadministration of rifampicin, a strong CYP3A4 inducer, decreased the AUC and C_{max} of tofacitinib by 84% and 74%, respectively (see Section 4.2 Dose and Method of Administration).

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



Abbreviations: AUC=total area under the concentration time curve; Cmax= maximum plasma concentration; CYP=cytochrome P450; PK=pharmacokinetics; CI=confidence interval
Note: Reference group is administration of tofacitinib alone
[a] In rheumatoid arthritis and psoriatic arthritis patients the recommended dose is XELJANZ 5 mg once daily. In ulcerative colitis patients the recommended dose is half the total daily dose indicated for patients not receiving these CYP inhibitors; in patients already taking XELJANZ 10 mg twice daily, reduce the dose to XELJANZ 5 mg twice daily, and in patients already taking XELJANZ 5 mg twice daily, reduce the dose to XELJANZ 5 mg once daily.

Potential for Tofacitinib to Influence the Pharmacokinetics of Other Medicines

In vitro studies indicate that tofacitinib does not significantly inhibit or induce the activity of the major human drug metabolising CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations exceeding 80 times the steady state C_{max} of a 10 mg twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the PK of midazolam, a highly sensitive CYP3A4 substrate, when coadministered with tofacitinib.

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

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 10 mg twice daily dose.

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

Oral Contraceptives

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

Methotrexate

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

Metformin

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

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

concentration time curve; Cmax= maximum plasma concentration; CYP=cytochrome P450; PK=pharmacokinetics; CI=confidence interval

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

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

Combination with Other Therapies

XELJANZ has not been studied and should not be used in combination with biological agents such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, selective co-stimulation modulators, and/or potent immunosuppressants such as azathioprine, 6-mercaptopurine, tacrolimus and cyclosporin because of the possibility of increased immunosuppression and increased risk of infection (see Section 4.3 Contraindications).

There was a higher incidence of adverse events for the combination of XELJANZ with MTX versus XELJANZ as monotherapy in RA clinical studies.

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

4.6 Fertility, Pregnancy and Lactation

Effects on fertility

In rats, tofacitinib had no effects on male fertility, sperm motility, or sperm concentration at doses up to 100 mg/kg/day (55 times the human unbound drug AUC at 10 mg twice daily; extrapolated from values from other rat studies). Treatment-related effects on female fertility were noted at ³ 10 mg/kg/day in rats (9 times the human unbound AUC at 10 mg twice daily; based on extrapolation from values from other rat studies).

Use in pregnancy

Category D

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

In an embryo-fetal development (EFD) study in rats given 30, 100, or 300 mg/kg/day, maternal toxicity was observed at doses ³ 100 mg/kg/day. Observations included postimplantation loss, consisting of early and late resorptions and consequently a reduced number of viable fetuses, and decreased uterine weight. Fetal developmental effects were observed at 100 mg/kg/day (³ 101 times the unbound drug human AUC at 10 mg twice daily). Teratogenic effects consisted of external and soft tissue malformations of anasarca and

membranous ventricular septal defects, respectively, and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). The no observed adverse effect level (NOAEL) for maternal and developmental toxicity in this study was 30 mg/kg/day, a dose at which the unbound drug AUC was ~40 times the human AUC at 10 mg twice daily.

In an EFD study in rabbits given 10, 30, or 100 mg/kg/day, maternal toxicity was not observed. Fetal developmental effects were observed at ≥30 mg/kg/day. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. The NOAELs for maternal and developmental toxicity in this study were 100 and 10 mg/kg/day, doses at which the total drug AUCs were ~32- and 1.5 times, respectively, the human AUC at 10 mg twice daily.

In a perinatal/postnatal rat study, there were reductions in live litter size, postnatal survival, and pup body weights at 50 mg/kg/day (~51 times the unbound exposure in humans at 5 mg twice daily, based on extrapolation from values from other rat studies). At 10 mg/kg/day (~12 times the unbound exposure in humans at 10 mg twice daily, based on extrapolation from values from other rat studies), no effect occurred on sexual maturation or the ability of the F1 generation rats to learn, mate, and produce viable F2 generation fetuses.

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

XELJANZ should not be used during pregnancy or by women attempting to become pregnant. Women of reproductive potential should be advised to use effective contraception both during treatment with XELJANZ and after discontinuing therapy. The extended pharmacodynamic effects of XELJANZ should be considered when determining how long to continue effective contraception after discontinuing XELJANZ therapy.

Use in lactation

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

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Adverse Effects (Undesirable Effects)

Rheumatoid Arthritis

The following data include 6 double-blind, controlled, multicentre studies of varying durations from 6 to 24 months (Studies I to VI, see Section 5.1 Pharmacodynamic Properties, Clinical Trials). In these studies, 3200 patients were randomised and treated with doses of

XELJANZ 5 mg twice daily (616 patients) or 10 mg twice daily (642 patients) monotherapy and XELJANZ 5 mg twice daily (973 patients) or 10 mg twice daily (969 patients) in combination with DMARDs (including MTX).

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

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

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

Psoriatic Arthritis

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

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

An additional long-term, open-label clinical trial was conducted which included 686 patients with PsA who originally participated in either of the 2 double-blind, controlled clinical trials. Patients who participated in this open-label clinical trial were initially treated with XELJANZ 5 mg twice daily. Starting at Month 1, escalation to XELJANZ 10 mg twice daily was permitted at investigator discretion; subsequent dose reduction to 5 mg twice daily was also permitted. This limits the interpretation of the long-term safety data with respect to dose.

Of the 783 patients who received XELJANZ doses of 5 mg twice daily or 10 mg twice daily in PsA clinical trials, 713 received treatment for 6 months or longer, of whom 635 received treatment for one year or longer, of whom 335 received treatment for greater than or equal to 24 months.

Ulcerative Colitis

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

Clinical Trial Experience

The most common category of serious adverse reactions in RA and PsA were serious infections (see Section 4.4 Special Warnings and Precautions For Use) and the most common categories of serious adverse reactions in UC were gastrointestinal disorders and infections..

Rheumatoid Arthritis

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 headache, upper respiratory tract infections, nasopharyngitis, diarrhoea, nausea and hypertension.

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

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

Body System / Adverse Event	XELJANZ 5 mg BD (N=1216)	XELJANZ 10 mg BD (N=1214)	Placebo (N=681)	Adalimumab 40 mg SC q2w (N=204)
Infections and Infestations				
Upper respiratory tract infection	53 (4.4)	47 (3.9)	23 (3.4)	7 (3.4)
Nasopharyngitis	48 (3.9)	35 (2.9)	19 (2.8)	7 (3.4)
Urinary tract infection	25 (2.1)	24 (2.0)	12 (1.8)	7 (3.4)
Bronchitis	14 (1.2)	13 (1.1)	10 (1.5)	4 (2.0)
Influenza	9 (0.7)	14 (1.2)	5 (0.7)	2 (1.0)
Herpes zoster	5 (0.4)	16 (1.3)	2 (0.3)	0
Blood and Lymphatic System Disorders				
Anaemia	15 (1.2)	13 (1.1)	8 (1.2)	0
Metabolism and Nutrition Disorders				
Hypercholesterolaemia	12 (1.0)	13 (1.1)	3 (0.4)	1 (0.5)
Nervous System Disorders				
Headache	54 (4.4)	39 (3.2)	15 (2.2)	5 (2.5)
Dizziness	13 (1.1)	12 (1.0)	8 (1.2)	3 (1.5)
Vascular Disorders				
Hypertension	20 (1.6)	27 (2.2)	7 (1.0)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	11 (0.9)	16 (1.3)	11 (1.6)	4 (2.0)
Gastrointestinal Disorders				
Diarrhoea	45 (3.7)	34 (2.8)	16 (2.3)	2 (1.0)
Nausea	32 (2.6)	25 (2.1)	18 (2.6)	3 (1.5)
Dyspepsia	19 (1.6)	25 (2.1)	11 (1.6)	3 (1.5)
Abdominal pain upper	23 (1.9)	13 (1.1)	5 (0.7)	3 (1.5)
Vomiting	21 (1.7)	9 (0.7)	10 (1.5)	0
Constipation	16 (1.3)	17 (1.4)	6 (0.9)	2 (1.0)
Gastritis	12 (1.0)	16 (1.3)	7 (1.0)	0
Abdominal pain	10 (0.8)	13 (1.1)	7 (1.0)	2 (1.0)
Gastroenteritis	12 (1.0)	13 (1.1)	5 (0.7)	0
Musculoskeletal and Connective Tissue Disorders				

Body System / Adverse Event	XELJANZ 5 mg BD (N=1216)	XELJANZ 10 mg BD (N=1214)	Placebo (N=681)	Adalimumab 40 mg SC q2w (N=204)
Rheumatoid arthritis	17 (1.4)	5 (0.4)	17 (2.5)	1 (0.5)
Back pain	18 (1.5)	20 (1.6)	5 (0.7)	1 (0.5)
Arthralgia	13 (1.1)	9 (0.7)	16 (2.3)	4 (2.0)
General Disorders and Administration Site Conditions				
Oedema peripheral	17 (1.4)	21 (1.7)	16 (2.3)	3 (1.5)
Pyrexia	13 (1.1)	7 (0.6)	5 (0.7)	1 (0.5)
Investigations				
Blood creatine phosphokinase increased	9 (0.7)	26 (2.1)	3 (0.4)	1 (0.5)
Alanine aminotransferase increased	14 (1.2)	15 (1.2)	7 (1.0)	1 (0.5)
Weight increased	11 (0.9)	13 (1.1)	4 (0.6)	2 (1.0)
Injury, Poisoning and Procedural Complications				
Fall	7 (0.6)	13 (1.1)	4 (0.6)	1 (0.5)

Abbreviations: BD=twice daily; SC q2w = subcutaneously once every 2 weeks.

Psoriatic Arthritis

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

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

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

Ulcerative Colitis

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

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

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

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

Overall, the safety profile observed in patients with UC treated with XELJANZ was consistent with the safety profile of XELJANZ in the RA indication.

Table 4 below lists the treatment-emergent adverse events (all causality) occurring in ≥2% of patients in any treatment group, during the Phase 2 and Phase 3 induction studies in the UC clinical program.

Table 4. Treatment-Emergent Adverse Events (All Causality) occurring in ³2% of patients in any treatment group during the Phase 2 and Phase 3 induction studies in the UC clinical program

SOC PT	Placebo (N = 282)	XELJANZ 10 mg BD (N = 938)
	n (%)	n (%)
Blood and lymphatic system disorders	**9 (3.19)**	**22 (2.35)**
Anaemia	9 (3.19)	22 (2.35)
Gastrointestinal disorders	**40 (14.18)**	**72 (7.68)**
Abdominal pain	11 (3.90)	25 (2.67)
Colitis ulcerative	20 (7.09)	26 (2.77)
Nausea	11 (3.90)	28 (2.99)
General disorders and administrative site conditions	**4 (1.42)**	**24 (2.56)**
Pyrexia	4 (1.42)	24 (2.56)
Infections and infestations	**20 (7.09)**	**82 (8.74)**
Nasopharyngitis	14 (4.96)	56 (5.97)
Upper respiratory tract infection	6 (2.13)	26 (2.77)
Investigations	**3 (1.06)**	**25 (2.67)**
Blood creatine phosphokinase increased	3 (1.06)	25 (2.67)
Elevated cholesterol levels*	0 (0.0)	31 (3.3)
Musculoskeletal and connective tissue disorders	**12 (4.26)**	**27 (2.88)**
Arthralgia	12 (4.26)	27 (2.88)
Nervous system disorders	**19 (6.74)**	**73 (7.78)**
Headache	19 (6.74)	73 (7.78)
Respiratory, thoracic and mediastinal disorders	**7 (2.48)**	**13 (1.39)**
Cough	7 (2.48)	13 (1.39)
Skin and subcutaneous tissue disorders	**1 (0.35)**	**25 (2.67)**
Acne	1 (0.35)	25 (2.67)

Abbreviations: BD = twice daily;; PT = preferred term; SOC = system organ class; UC = ulcerative colitis.
Subjects are only counted once per treatment for each row.
*includes: hypercholesterolaemia, hyperlipidaemia, blood cholesterol increased, dyslipidaemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased.

Maintenance Trial (Study UC-III)

Common adverse reactions reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported in patients receiving placebo are shown in Table 5.

Table 5: Common Adverse Reactions* in UC Patients during the Maintenance Trial (Study UC-III)

Preferred Term	**XELJANZ 5 mg Twice Daily**	**XELJANZ 10 mg Twice Daily**	**Placebo**
	N = 198 (%)	**N = 196 (%)**	**N = 198 (%)**
Nasopharyngitis	10	14	6
Elevated cholesterol levels**	5	9	1
Headache	9	3	6
Upper respiratory tract infection	7	6	4
Increased blood creatine phosphokinase	3	7	2
Rash	3	6	4
Diarrhoea	2	5	3
Herpes zoster	1	5	1
Gastroenteritis	3	4	3
Anaemia	4	2	2
Nausea	1	4	3

* reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported for placebo.

** includes hypercholesterolaemia, hyperlipidaemia, blood cholesterol increased, dyslipidaemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased.

In the 52-week maintenance study, no malignancies were reported in patients treated with XELJANZ 10 mg twice daily or 5 mg twice daily. In the long-term extension study, malignancies (including solid cancers, lymphomas and NMSC) were observed more often in patients treated with XELJANZ 10 mg twice daily (see Section 4.4 Special Warnings and Precautions For Use). Four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one fatality in a patient with advanced cancer.

Dose-dependent adverse reactions seen across indications in patients treated with XELJANZ 10 mg twice daily, in comparison to 5 mg twice daily, include the following: herpes zoster infections (incidence rates in UC patients for 10 mg twice daily and 5 mg twice daily were 6.64 events per 100 patient-years and 2.05 events per 100 patient-years, respectively), serious infections (incidence rates in UC patients for 10 mg twice daily and 5 mg twice daily were 0.64 events per 100 patient-years and 1.35 events per 100 patient-years, respectively), and NMSC (incidence rates in UC patients for 10 mg twice daily and 5 mg twice daily were 1.91 events per 100 patient-years and 0 events per 100 patient years, respectively)(see Section 4.4 Special Warnings and Precautions For Use).

Adverse Drug Reactions for XELJANZ

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

Blood and Lymphatic System Disorders

Common: Anaemia.

Uncommon: Leucopenia, lymphopenia, neutropenia.

Gastrointestinal Disorders

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

General Disorders and Administration Site Conditions

Common: Pyrexia, oedema peripheral, fatigue.

Hepatobiliary Disorders

Uncommon: Hepatic steatosis.

Infections and Infestations

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

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

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

Injury, Poisoning and Procedural Complications

Uncommon: Ligament sprain**,** muscle strain

Investigations

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

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

Metabolism and Nutrition Disorders

Common: Hyperlipidaemia.

Uncommon: Dyslipidaemia, dehydration.

Musculoskeletal and Connective Tissue Disorders

Common: Arthralgia.

Uncommon: Musculoskeletal pain, tendonitis, joint swelling.

Neoplasm Benign, Malignant and Unspecified (Including Cysts and Polyps)

Uncommon: Nonmelanoma skin cancers.[§]

Nervous System Disorders

Common: Headache.

Uncommon: Paraesthesia.

Psychiatric Disorders

Uncommon: Insomnia.

Respiratory, Thoracic and Mediastinal Disorders

Common: Cough.

Uncommon: Dyspnoea, sinus congestion.

Skin and Subcutaneous Tissue Disorders

Common: Rash.

Uncommon: Erythema, pruritus.

Vascular Disorders

Common: Hypertension.

^ These ADRs have only been reported in open-label long-term extension studies; therefore, the frequency of these ADRs in Phase 3 randomised trials was estimated.

§ Nonmelanoma skin cancer is not a preferred term. The frequency is determined by combining frequencies for the PT's of basal cell carcinoma and squamous cell carcinoma.

Overall Infections

Rheumatoid Arthritis

In the controlled portion (0-3 months) of the phase 3 monotherapy studies (I and VI), the rate of infections in the 5 mg twice daily and 10 mg twice daily XELJANZ monotherapy groups were 16.1% and 17.8%, respectively, compared to 18.9% in the placebo group. In the controlled portion (0-3 months) of the phase 3 studies II to V with background DMARDs, the rates of infections in the 5 mg twice daily and 10 mg twice daily XELJANZ plus DMARD groups were 21.3% and 21.8%, respectively, compared to 18.4% in the placebo plus DMARD group. In the controlled portion (0-6 months) of the phase 3 studies II to IV with background DMARDs, the rates of infections in the 5 mg twice daily and 10 mg twice daily XELJANZ plus DMARD groups were 34.6% and 32.8%, respectively, compared to 21.3% in the placebo plus DMARD group.

The most commonly reported infections were upper respiratory tract infections and nasopharyngitis (3.7% and 3.2%, respectively).

The overall rate of infections with XELJANZ in the long-term safety all exposure population (total 4867 patients) was 72.1 events per 100 patient-years (71.8 and 72.2 events for 5 mg and 10 mg twice daily, respectively). For patients on monotherapy (total 1750), the rates were 75.3 and 64.2 events per 100 patient-years for 5 mg and 10 mg twice daily, respectively. For patients on background DMARDs (total 3117), the rates were 69.7 and 76.5 events per 100 patient-years for 5 mg and 10 mg twice daily, respectively.

Psoriatic Arthritis

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

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

The overall rate of infections with XELJANZ in the long-term safety population for combined doses was 52.3 patients with events per 100 patient-years.

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 twice daily 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 twice daily and 39.8% (78 patients) in the 10 mg twice daily XELJANZ groups, compared to 24.2% (48 patients) in the placebo group.

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

In the entire treatment experience with XELJANZ, the overall incidence rate of infections was 60.3 events per 100 patient-years (involving 49.4% of patients; total 572 patients).

Serious Infections

Rheumatoid Arthritis

In the controlled portion (0-3 months) of the phase 3 monotherapy studies (I and VI), the rate of serious infections in the 5 mg twice daily XELJANZ monotherapy group was 0.2% (0.7 events per 100 patient-years). In the 10 mg twice daily XELJANZ monotherapy group, the rate was 0.3% (1.3 events per 100 patient-years), and the rate was 0 for the placebo group.

In the controlled portion (0-3 months) of the phase 3 studies II to V with background DMARDs, the rates of serious infections in the 5 mg twice daily and 10 mg twice daily XELJANZ plus DMARD groups were 0.8% and 0.8% (4.4 and 3.9 events per 100 patient-years), respectively, compared to 0.4% (1.5 events per 100 patient-years) in the placebo plus DMARD group. In the controlled portion (0-6 months) of the phase 3 studies II to IV with background DMARDs, the rates of serious infections in the 5 mg twice daily and 10 mg twice daily XELJANZ plus DMARD groups were 1.8% and 1.4% (4.7 and 3.4 events per 100 patient-years), respectively, compared to 0.5% (2.1 events per 100 patient-years) in the placebo plus DMARD group.

In the long-term safety all exposure population, the overall rates of serious infections were 2.7 and 3.4 events per 100 patient-years in the 5 mg and 10 mg twice daily XELJANZ groups, respectively. The most common serious infections reported with XELJANZ included pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis and diverticulitis. Cases of opportunistic infections have been reported (see Section 4.4 Special Warnings and Precautions For Use).

Serious infections in the elderly

Of the 4271 patients who enrolled in Studies I to VI, a total of 608 RA patients were 65 years of age and older, including 85 patients 75 years and older. The frequency of serious infection among XELJANZ-treated patients 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly (see Section 4.4 Special Warnings and Precautions For Use).

Psoriatic Arthritis

In the 6-month and 12-month Phase 3 studies, the rate of serious infections in the XELJANZ 5 mg twice daily group was 1.30 patients with events per 100 patient-years. In the XELJANZ 10 mg twice daily group, the rate was 2.0 patients with events per 100 patient-years.

In the long-term safety population, the overall rate of serious infections was 1.4 patients with events per 100 patient-years for XELJANZ treated patients. The most common serious infection reported with XELJANZ was pneumonia.

Ulcerative Colitis

In the randomised 8-week Phase 2/3 induction studies, the proportion of patients with serious infections in patients treated with XELJANZ 10 mg twice daily was 0.9% (8 patients) compared with 0.0% in patients treated with placebo. In the randomised 52-week Phase 3 maintenance study, the incidence rates of serious infections in patients treated with XELJANZ 5 mg twice daily (1.35 events per 100 patient-years) and in patients treated with XELJANZ 10 mg twice daily (0.64 events per 100 patient-years) were not higher than that for placebo (1.94 events per 100 patient-years). The incidence rate of serious infections in the entire treatment experience with XELJANZ in patients with UC was 1.99 events per 100 patient-years. There was no apparent clustering into specific types of serious infections.

Viral Reactivation

Patients treated with XELJANZ who are Japanese or Korean, or patients with long standing RA who have previously received two or more biological DMARDs, or patients with an ALC less than 1.0×10^9 cells/L, or patients treated wth 10 mg twice daily may have an increased risk of herpes zoster (see Section 4.4 Special Warnings and Precautions For Use).

Laboratory Parameters

In the clinical trials in PsA and UC, changes in lymphocytes, neutrophils, and lipids observed with XELJANZ treatment were similar to the changes observed in clinical trials in RA.

In the clinical trials in PsA and UC, changes in liver enzyme tests observed with XELJANZ treatment were similar to the changes observed in clinical trials in RA where patients received background DMARDs.

Rheumatoid Arthritis

Lymphocytes

In the controlled RA clinical studies, confirmed decreases in ALC below 0.5×10^9 cells/L occurred in 0.3% of patients and for ALC between 0.5 and 0.75×10^9 cells/L in 1.9% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

In the RA long term safety population, confirmed decreases in ALC below 0.5×10^9 cells/L occurred in 1.3% of patients and for ALC between 0.5 and 0.75×10^9 cells/L in 8.4% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

Confirmed ALC less than 0.75 x 10^9 cells/L were associated with an increased incidence of serious infections (see Section 4.4 Special Warnings and Precautions For Use and Section 4.2 Dose and Method of Administration).

Neutrophils

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

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

Liver Enzyme Tests

Confirmed increases in liver enzymes ≥3x upper limit of normal (ULN) were uncommonly observed. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of XELJANZ, or reduction in XELJANZ dose, resulted in decrease or normalisation of liver enzymes.

In the controlled portion of the phase 3 placebo-controlled monotherapy study (0-3 months) (Study I, see Section 5.1 Pharmacodynamic Properties, Clinical Trials), ALT elevations ≥ 3x ULN were observed in 1.65%, 0.41%, and 0% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively. In this study, AST elevations ≥ 3x ULN were observed in 1.65%, 0.41% and 0% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively.

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

In the controlled portion of the phase 3 studies on background DMARDs (0-3 months) (Studies II-V, see Section 5.1 Pharmacodynamic Properties, Clinical Trials), ALT elevations ≥ 3x ULN were observed in 0.9%, 1.24% and 1.14% of patients receiving placebo, XELJANZ 5 mg, and 10 mg twice daily, respectively. In these studies, AST elevations ≥ 3x ULN were observed in 0.72%, 0.52% and 0.31% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively.

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

Lipids

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

- Mean LDL cholesterol increased by 15% in the XELJANZ 5 mg twice daily arm and 20% in the XELJANZ 10 mg twice daily arm at month 12, and increased by 16% in the XELJANZ 5 mg twice daily arm and 19% in the XELJANZ 10 mg twice daily arm at month 24.

- Mean HDL cholesterol increased by 17% in the XELJANZ 5 mg twice daily arm and 18% in the XELJANZ 10 mg twice daily arm at month 12, and increased by 19% in the XELJANZ 5 mg twice daily arm and 20% in the XELJANZ 10 mg twice daily arm at month 24.

- Mean LDL cholesterol/HDL cholesterol ratios were essentially unchanged in XELJANZ-treated patients.

- Apolipoprotein B (ApoB)/ApoA1 ratios were essentially unchanged in XELJANZ-treated patients.

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

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

Serum Creatinine

In the controlled clinical trials, dose-related elevations in serum creatinine were observed with XELJANZ treatment. The mean increase in serum creatinine was <8.84 µmol/L in the 12-month pooled safety analysis; however, with increasing duration of exposure in the long-term extensions, up to 2.4% of patients were discontinued from 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.

Post-Marketing Experience

Immune system disorders

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

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

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

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of action

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

Pharmacodynamics

In patients with RA, treatment up to 6 months with tofacitinib was associated with dose-dependent reductions of circulating CD16/56+ natural killer (NK) cells, with estimated maximum reductions occurring at approximately 8-10 weeks after initiation of therapy. These changes generally resolved within 2-6 weeks after discontinuation of treatment. Treatment with tofacitinib was associated with dose-dependent increases in B cell counts. Changes in circulating T-lymphocyte counts and T-lymphocyte subsets (CD3+, CD4+ and CD8+) were small and inconsistent.

Following long-term treatment (median duration of tofacitinib treatment of approximately 5 years), CD4+ and CD8+ counts showed median reductions of 28% and 27%, respectively, from baseline. In contrast to the observed decrease after short-term dosing, CD16/56+ NK

cell counts showed a median increase of 73% from baseline. CD19+ B cell counts showed no further increases after long term tofacitinib treatment. These changes returned toward baseline after temporary discontinuation of treatment. There was no evidence of an increased risk of serious or opportunistic infections or herpes zoster at low values of CD4+, CD8+ or NK cell counts or high B cell counts.

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 (see Section 4.4 Special Warnings and Precautions For Use, Serious Infections and Section 4.2 Dose and Method of Administration).

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

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

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.

Clinical trials

Rheumatoid Arthritis

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

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

Study II (A3921046/ORAL Sync) was a 12-month study in which 792 patients with moderate to severe active RA who had an inadequate response to a csDMARD received XELJANZ

5 mg or 10 mg twice daily or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). At the Month 3 visit, nonresponding patients randomised to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of XELJANZ 5 mg or 10 mg twice daily. At the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3 and rates of DAS28-4(ESR)<2.6 at Month 6.

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

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

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

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

Clinical Response

ACR Response

The percentages of XELJANZ-treated patients achieving ACR20, ACR50 and ACR70 responses in Studies I, II, III, IV, and V are shown in Table 6. Results are provided for XELJANZ 5 mg twice daily.

In Studies I and V, patients treated with 5 mg twice daily 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 twice daily XELJANZ had statistically

superior ACR20, ACR50, and ACR70 response rates at Months 3 and 6 vs placebo-treated patients (Table 6).

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

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

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

DAS28-4 (ESR) Response

Patients in the Phase 3 studies had a mean Disease Activity Score (DAS28-4(ESR)) of 6.1–6.7 at baseline. Significant reductions in DAS28-4(ESR) from baseline (mean improvement) of 1.8-2.0 were observed in 5 mg XELJANZ-treated patients compared to placebo-treated patients (0.7-1.1) at 3 months. The proportion of patients achieving a DAS28 clinical remission (DAS28-4(ESR)<2.6) in Studies II, III and IV was significantly higher in patients receiving 5 mg XELJANZ (6–9%) compared to placebo (1–3%) patients at 6 months. In Study III, the percentages of patients achieving DAS28-4(ESR)<2.6 observed for XELJANZ 5 mg twice daily and adalimumab at Month 6 were 6.2% and 6.7%, respectively.

Table 6: Proportion of Patients with an ACR Response

	Percent of Patients										
	Monotherapy in DMARD Inadequate Responders		**DMARD Inadequate Responders**		**MTX Inadequate Responders**			**MTX Inadequate Responders**		**TNF Inhibitor Inadequate Responders**	
	Study I (SOLO)		**Study II (SYNC)**		**Study III (Standard)**			**Study IV (SCAN)**		**Study V (STEP)**	
Response Rate	Placebo N=120	XELJANZ 5 mg Twice Daily N=241	Placebo + DMARD N=157	XELJANZ 5 mg Twice Daily + DMARD N=311	Placebo + MTX N=106	XELJANZ 5 mg Twice Daily + MTX N=196	Adalimumab 40 mg q2 Weeks + MTX N=199	Placebo + MTX N=154	XELJANZ 5 mg Twice Daily + MTX N=309	Placebo + MTX N=131	XELJANZ 5 mg Twice Daily + 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%
Month 12	NA	NA	NA	51%	NA	49%	49%	NA	49%	NA	NA
Month 24	NA	NA	NA	NA	NA	NA	NA	NA	41%	NA	NA
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%
Month 12	NA	NA	NA	33%	NA	37%	34%	NA	32%	NA	NA
Month 24	NA	NA	NA	NA	NA	NA	NA	NA	29%	NA	NA
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%
Month 12	NA	NA	NA	19%	NA	23%	17%	NA	19%	NA	NA
Month 24	NA	NA	NA	NA	NA	NA	NA	NA	17%	NA	NA

* *p<0.05,* XELJANZ *vs. placebo*
** *p<0.001,* XELJANZ *vs. placebo*
*** *p<0.0001,* XELJANZ *vs. placebo*

Abbreviations: ACR20/50/70=American College of Rheumatology ≥ 20, 50, 70% improvement; DMARD=disease-modifying antirheumatic drug; MTX=methotrexate; q2 Weeks=once every 2 weeks; NA=Not applicable.

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

Table 7: Components of ACR Response at Month 3

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

Abbreviations: MTX=methotrexate; TNF=tumour necrosis factor; CRP=C-reactive protein.

[a]Visual analog scale: 0 = best, 100 = worst

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

The percent of ACR20 responders by visit for Study IV is shown in Figure 3. Similar responses were observed in Studies I, II, III and V.

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

Abbreviations: ACR20=American College of Rheumatology ≥ 20% improvement

Radiographic Response

In Study IV, progression of structural joint damage was assessed radiographically and expressed as change from baseline in mTSS and its components, the erosion score and joint space narrowing (JSN) score, at Months 6 and 12. The proportion of patients with no radiographic progression (mTSS change less than or equal to 0.5) was also assessed. XELJANZ 5 mg twice daily plus background MTX lead to a change of -0.3 in the progression of structural damage compared to placebo plus MTX at Month 6 but the result was not statistically significant. In the placebo plus MTX group, 78% of patients experienced no radiographic progression at Month 6 compared to 89% of patients treated with XELJANZ 5 mg twice daily plus MTX.

In Study VI, XELJANZ monotherapy inhibited the progression of structural damage compared to MTX at Months 6 and 12 in MTX-naïve patients (mean difference in mTSS from MTX was -0.7 and -0.9 respectively), which was maintained at Month 24. Analyses of erosion and JSN scores were consistent with overall results. Significantly more patients in the

XELJANZ 5 mg twice daily group experienced no radiographic progression at Month 6 (84%) compared to patients in the MTX group (70%). XELJANZ is not approved for use in MTX-naïve patients.

Physical Function Response and Health Related Outcomes

Improvements in physical function have been shown with and without MTX.

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg twice daily demonstrated significantly greater improvement from baseline in physical functioning compared to placebo at Month 3 (Studies I, II, III, and V) and Month 6 (Studies II and III). XELJANZ 5 mg twice daily treated patients exhibited significantly greater improved physical functioning compared to placebo as early as Week 2 in Studies I and II. Compared with adalimumab-treated patients, at Month 3, patients in the XELJANZ 5 mg twice daily group had similar decreases from baseline in HAQ-DI values. The mean change in HAQ-DI from baseline to Month 3 in Studies I to V are shown in Table 8.

Table 8: Mean Change from Baseline in HAQ-DI

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

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

Health-related quality of life was assessed by the Short Form Health Survey (SF-36) in all 5 studies. XELJANZ-treated patients exhibited significantly greater improvement from baseline compared to placebo in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS) at Month 3 in Studies I, IV, and V. In Studies III and IV, mean SF-36 improvements were maintained to 12 months in XELJANZ-treated patients.

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

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

Durability of Clinical Responses

Durability of effect was assessed by ACR20, ACR50, ACR70 response rates, mean HAQ-DI, and mean DAS28-4(ESR) in the three Phase 3 DMARD IR studies with duration of at least one year (studies II, III and IV). Efficacy was maintained through to the end of the studies.

Evidence of persistence of efficacy with tofacitinib treatment for up to 7 years is also provided from data in the one ongoing and one completed open-label, long-term follow-up studies.

Psoriatic arthritis

The efficacy and safety of XELJANZ were assessed in 2 randomised, double-blind, placebo-controlled Phase 3 studies in adult patients with active PsA (≥ 3 swollen and ≥ 3 tender joints); patients received 1 csDMARD as concomitant therapy. Patients with each subtype of PsA were enrolled in these studies including: polyarticular arthritis, < 5 joints or asymmetric involvement, distal interphalangeal (DIP) joint involvement, arthritis mutilans and spondylitis with peripheral arthritis. The median PsA disease duration was 5.5 years. Patients were required to have active plaque psoriasis at the screening visit. At baseline, 80% and 53% of patients had enthesitis and dactylitis, respectively. For both studies, the primary endpoints were ACR20 response rate and change from baseline in HAQ-DI at Month 3.

Study PsA-I (OPAL BROADEN) evaluated 422 patients who had a previous inadequate response (due to lack of efficacy or intolerance) to a csDMARD (MTX for 92.7% of patients); 32.7% of the patients in this study had a previous inadequate response to > 1 csDMARD or 1 csDMARD and a targeted synthetic DMARD (tsDMARD). In OPAL BROADEN, previous treatment with TNF inhibitor was not allowed. All patients were required to have 1 concomitant csDMARD; 83.9% of patients received concomitant MTX. Patients randomised to XELJANZ received 5 mg twice daily or XELJANZ 10 mg twice daily for 12 months. Patients randomised to placebo were advanced in a blinded manner at Month 3 to either XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily and received treatment until Month 12. Patients randomised to adalimumab (active-control arm) received 40 mg subcutaneously every 2 weeks for 12 months.

Study PsA-II (OPAL BEYOND) evaluated 394 patients who had discontinued a TNF inhibitor due to lack of efficacy or intolerance; 36.0% had a previous inadequate response to > 1 biological DMARD. All patients were required to have 1 concomitant csDMARD; 71.6% of patients received concomitant MTX. Patients randomised to XELJANZ received 5 mg twice daily or XELJANZ 10 mg twice daily for 6 months. Patients randomised to placebo were advanced in a blinded manner at Month 3 to either XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily and received treatment until Month 6.

Signs and symptoms

Treatment with XELJANZ resulted in significant improvements in the signs and symptoms of PsA, as assessed by the ACR20 response criteria compared to placebo at Month 3. The efficacy results for other important endpoints assessed are shown in Table 9.

Table 9: Proportion (%) of PsA Patients Who Achieved Clinical Response and Mean Change from Baseline in OPAL BROADEN and OPAL BEYOND Studies

	csDMARD Inadequate Responders[a] (TNFi-Naïve)			TNFi Inadequate Responders[b]	
	OPAL BROADEN			OPAL BEYOND[c]	
Treatment Group	**Placebo**	**XELJANZ 5 mg Twice Daily**	**Adalimumab 40 mg SC q2W**	**Placebo**	**XELJANZ 5 mg Twice Daily**
N	105	107	106	131	131
ACR20					
Month 3	33%	50%[d,*]	52%[*]	24%	50%[d,***]
Month 6	NA	59%	64%	NA	60%
Month 12	NA	68%	60%	-	-
ACR50					
Month 3	10%	28%[e,**]	33%[***]	15%	30%[e,*]
Month 6	NA	38%	42%	NA	38%
Month 12	NA	45%	41%	-	-
ACR70					
Month 3	5%	17%[e,*]	19%[*]	10%	17%
Month 6	NA	18%	30%	NA	21%
Month 12	NA	23%	29%	-	-
ΔLEI[f]					
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[f]					
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[g]					
Month 3	15%	43%[d,***]	39%[**]	14%	21%
Month 6	NA	46%	55%	NA	34%
Month 12	NA	56%	56%	-	-

[*] Nominal p≤0.05, [**] Nominal p<0.001, [***]Nominal p<0.0001 for active treatment versus placebo at Month 3.

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 at least 1 TNFi due to lack of efficacy and/or intolerability.

[c] OPAL BEYOND had a duration of 6 months.

[d] Achieved statistical significance globally at p≤ 0.05 per the pre-specified step-down testing procedure.

[e] Achieved statistical significance within the ACR family (ACR50 and ACR70) at p≤ 0.05 per the pre-specified step-down testing procedure.

f For patients with Baseline score > 0.

g For patients with Baseline BSA ≥ 3% and PASI > 0.

Both TNF inhibitor naïve and TNF inhibitor inadequate responder XELJANZ-treated patients had significantly higher ACR20 response rates compared to placebo at Month 3. Examination of age, sex, race, baseline disease activity and PsA subtype did not identify differences in response to XELJANZ. The number of patients with arthritis mutilans was too small to allow meaningful assessment.

As with the ACR responses, in patients treated with XELJANZ 5 mg twice daily in OPAL BROADEN and OPAL BEYOND, 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 10).

Table 10: Components of ACR Response at Baseline and Month 3 in OPAL BROADEN and OPAL BEYOND Studies

	csDMARD Inadequate Responders[d] (TNFi-Naïve)			TNFi Inadequate Responders[e]	
	OPAL BROADEN			OPAL BEYOND	
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

Abbreviations: ACR=American College of Rheumatology; csDMARD=conventional synthetic disease-modifying antirheumatic drug; N=number of randomised and treated patients; SC q2w=subcutaneously once every 2 weeks; TNFi=tumour necrosis factor inhibitor; CRP=C-reactive protein

[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

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

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

ACR20 response rates for patients receiving tofacitinib 5 mg twice daily were statistically significantly higher than those receiving placebo as early as Week 2 (first post-baseline assessment).

ACR response rates, as well as effects on other endpoints (skin manifestations, enthesitis and dactylitis) continued to improve or were maintained through Month 6 (OPAL BROADEN and OPAL BEYOND) and Month 12 (OPAL BROADEN).

In OPAL BROADEN, resolution of enthesitis at Month 3 occurred in 33.3%, 47.4%, and 21.5% of patients on XELJANZ 5 mg twice daily, adalimumab 40 mg subcutaneously once every 2 weeks, and placebo, respectively. In OPAL BEYOND, resolution of enthesitis at Month 3 occurred in 39.8% and 21.6% of patients on XELJANZ 5 mg twice daily and placebo, respectively.

In Study OPAL BROADEN, resolution of dactylitis at Month 3 occurred in 34.4%, 46.6%, and 32.8% of patients on XELJANZ 5 mg twice daily, adalimumab 40 mg subcutaneously once every 2 weeks, and placebo, respectively. In OPAL BEYOND, resolution of dactylitis at Month 3 occurred in 51.5% and 28.6% of patients on XELJANZ 5 mg twice daily and placebo, respectively.

Improvements were observed after treatment with XELJANZ on the Minimum Disease Activity (MDA) response rate and the Psoriatic Arthritis Disease Activity Score (PASDAS).

Radiographic response

In Study OPAL BROADEN, the progression of structural joint damage was assessed radiographically utilising the van der Heijde modified Total Sharp Score (mTSS) and the proportion of patients with radiographic progression (mTSS increase from baseline greater than 0.5) was assessed at Month 12. At Month 12, 96% and 98% of patients receiving XELJANZ 5 mg twice daily and adalimumab 40 mg subcutaneously every 2 weeks, respectively, did not have radiographic progression (mTSS increase from baseline less than or equal to 0.5).

Physical function and health-related quality of life

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg twice daily demonstrated greater improvement ($p \leq 0.05$) from baseline in physical functioning compared to placebo at Month 3 (see Table 11). HAQ-DI improvement from baseline in XELJANZ-treated patients was maintained or improved through Month 6 (OPAL BROADEN and OPAL BEYOND) and Month 12 (OPAL BROADEN).

Table 11: Change From Baseline in HAQ-DI in PsA Studies OPAL BROADEN and OPAL BEYOND

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

[*] Nominal p≤0.05; [***] Nominal p<0.0001 for active treatment versus placebo at Month 3.

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.

[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] Achieved statistical significance globally at p≤ 0.05 per the pre-specified step-down testing procedure.

The HAQ-DI responder rate (response defined as having decrease from baseline of ≥ 0.35) at Month 3 in Studies OPAL BROADEN and OPAL BEYOND 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 (OPAL BROADEN only).

Health-related quality of life was assessed by SF-36v2. Patients receiving XELJANZ 5 mg twice daily demonstrated greater improvement from baseline compared to placebo in the physical functioning domain and the physical component summary score at Month 3 in Studies OPAL BROADEN and OPAL BEYOND (nominal p≤ 0.05). Improvements from baseline in SF-36v2 were maintained or improved through Month 6 (OPAL BROADEN and OPAL BEYOND) and Month 12 (OPAL BROADEN).

Improvement in fatigue was evaluated by the FACIT-F. Patients receiving XELJANZ 5 mg twice daily demonstrated greater improvements from baseline in FACIT-F scores compared to placebo at Month 3 in Studies OPAL BROADEN and OPAL BEYOND (nominal p≤ 0.05). Improvements from baseline in FACIT-F scores were maintained or improved up to Month 6 (OPAL BROADEN and OPAL BEYOND) and Month 12 (OPAL BROADEN).

Improvement in pain was assessed by the Patient's Assessment of Arthritis Pain on a 0 to 100 Visual Analogue Scale (PAAP VAS). Patients receiving XELJANZ 5 mg twice daily demonstrated a greater reduction in pain from baseline in the PAAP VAS score compared to placebo at Month 3; this was seen as early as Week 2 in Studies OPAL BROADEN and OPAL BEYOND (nominal p≤ 0.05). Improvement from baseline in PAAP VAS scores was maintained up to Month 6 (OPAL BROADEN and OPAL BEYOND) and Month 12 (OPAL BROADEN).

Ulcerative Colitis

Induction Studies (OCTAVE Induction 1 and OCTAVE Induction 2)

In two identical induction trials (OCTAVE Induction 1 / Study UC-I and OCTAVE Induction 2 / Study UC-II), 1139 patients were randomised (598 and 541 patients, respectively) to XELJANZ 10 mg twice daily or placebo with a 4:1 treatment allocation ratio. A total of 52%, 73% and 72% of patients had previously failed or were intolerant to TNF blockers, corticosteroids, and/or immunosuppressants, respectively. Oral corticosteroids were received as concomitant treatment for UC by 47% of patients and 71% were receiving concomitant aminosalicylates as treatment for UC. The baseline clinical characteristics were generally similar between the XELJANZ treated patients and patients receiving placebo.

The disease activity was assessed by Mayo scoring index (0 to 12) which consists of four subscores (0 to 3 for each subscore): stool frequency, rectal bleeding, findings on endoscopy, and physician global assessment. An endoscopy subscore of 2 was defined by marked erythema, absent vascular pattern, any friability, and erosions; an endoscopy subscore of 3 was defined by spontaneous bleeding and ulceration.

The primary endpoint of OCTAVE Induction 1 and OCTAVE Induction 2 was the proportion of patients in remission at Week 8, and the key secondary endpoint was the proportion of patients with improvement of endoscopic appearance of the mucosa at Week 8. Remission was defined as clinical remission (a total Mayo score ≤ 2 with no individual subscore > 1) and rectal bleeding subscore of 0. Improvement of endoscopic appearance of the mucosa was defined as endoscopy subscore of 0 or 1.

The other secondary efficacy endpoints were clinical response at Week 8 and normalisation of endoscopic appearance of the mucosa at Week 8. Clinical response was defined as a decrease from baseline in Mayo score of ≥ 3 points and $\geq 30\%$, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 point or absolute subscore for rectal bleeding of 0 or 1. Normalisation of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0.

A significantly greater proportion of patients treated with XELJANZ 10 mg twice daily achieved remission, improvement of endoscopic appearance of the mucosa, and clinical response at Week 8 compared to placebo in both studies, as shown in Table 12.

The efficacy results based on the endoscopic readings at the study sites were consistent with the results based on the central endoscopy readings.

Table 12: Proportion of Patients Meeting Efficacy Endpoints at Week 8 (OCTAVE Induction Study 1 and OCTAVE Induction Study 2)

	OCTAVE Induction Study 1			
	Central Endoscopy Read		**Local Endoscopy Read**	
	Placebo	**XELJANZ**	**Placebo**	**XELJANZ**

Endpoint		**10 mg Twice daily**		**10 mg Twice daily**
	N=122	**N=476**	**N=122**	**N=476**
Remission[a]	8.2%	18.5%‡	11.5%	24.8%‡
Improvement of endoscopic appearance of the mucosa[b]	15.6%	31.3%†	23.0%	42.4%*
Normalisation of endoscopic appearance of the mucosa[c]	1.6%	6.7%‡	2.5%	10.9%‡
Clinical response[d]	32.8%	59.9%*	34.4%	60.7%*
	OCTAVE Induction Study 2			
	Central Endoscopy Read		**Local Endoscopy Read**	
Endpoint	**Placebo**	**XELJANZ 10 mg Twice daily**	**Placebo**	**XELJANZ 10 mg Twice daily**
	N=112	**N=429**	**N=112**	**N=429**
Remission[a]	3.6%	16.6%†	5.4%	20.7%†
Improvement of endoscopic appearance of the mucosa[b]	11.6%	28.4%†	15.2%	36.4%*
Normalisation of endoscopic appearance of the mucosa[c]	1.8%	7.0%‡	0.0%	9.1%‡
Clinical response[d]	28.6%	55.0%*	29.5%	58.0%*

* $p<0.0001$; † $p<0.001$; ‡ $p<0.05$.

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).

c. Normalisation of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0.

d. 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.

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 13).

Table 13. Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 8 by TNF Inhibitor Therapy Subgroups (OCTAVE Induction Study 1 and OCTAVE Induction Study 2, Central Endoscopy Read)

	OCTAVE Induction Study 1		**OCTAVE Induction Study 2**	
Endpoint	**Placebo N=122**	**XELJANZ 10 mg twice daily N=476**	**Placebo N=112**	**XELJANZ 10 mg twice daily N=429**
Remission[a]				
With prior TNF inhibitor failure	1.6% (1/64)	11.1% (27/243)	0.0% (0/60)	11.7% (26/222)
Without prior TNF inhibitor failure[b]	15.5% (9/58)	26.2% (61/233)	7.7% (4/52)	21.7% (45/207)
Improvement of endoscopic appearance of the mucosa[c]				
With prior TNF inhibitor failure	6.3% (4/64)	22.6% (55/243)	6.7% (4/60)	21.6% (48/222)
Without prior TNF inhibitor failure[b]	25.9% (15/58)	40.3% (94/233)	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. Included TNF Inhibitor naïve patients

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).

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

Maintenance (OCTAVE Sustain)

Patients who completed 8 weeks in 1 of the induction studies and achieved clinical response were re-randomised into OCTAVE Sustain (Study UC-III); 179 out of 593 (30.2%) patients were in remission at baseline of OCTAVE Sustain.

The primary endpoint in OCTAVE Sustain 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 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 proportion of patients in both the XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily treatment groups achieved the following endpoints at Week 52 as compared to placebo: remission, improvement of endoscopic appearance of the mucosa, normalization of endoscopic appearance of the mucosa, maintenance of clinical response, remission among patients in remission at baseline, and sustained corticosteroid-free remission at both Week 24 and Week 52 among patients in remission at baseline.

In both subgroups of patients with or without prior TNF inhibitor failure, a greater proportion of patients treated with either XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily achieved the following endpoints at Week 52 of OCTAVE Sustain as compared to placebo: remission, improvement of endoscopic appearance of the mucosa, or sustained corticosteroid-free remission at both Week 24 and Week 52 among patients in remission at baseline (Table 14). This treatment difference from placebo was similar between XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily in the subgroup of patients without prior TNF inhibitor failure. In the subgroup of patients with prior TNF inhibitor failure, the observed treatment difference from placebo was numerically greater for XELJANZ 10 mg twice daily than XELJANZ 5 mg twice daily by 9.7 to 16.7 percentage points across the primary and key secondary endpoints.

Table 14. Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints in Maintenance OCTAVE Sustain (Central Endoscopy Read)

				Treatment Difference versus Placebo (95% CI)	
Endpoint	**Placebo**	**XELJANZ 5 mg Twice Daily**	**XELJANZ 10 mg Twice Daily**	**XELJANZ 5 mg Twice Daily**	**XELJANZ 10 mg Twice Daily**
Remission at Week 52[a]					
Total Population	N=198 11%	N=198 34%	N=197 41%	23%* (15.3, 31.2)	30%* (21.4, 37.6)
With Prior TNF Inhibitor Failure[b]	N=89 11%	N=83 24%	N=93 37%		
Without Prior TNF Inhibitor Failure[c]	N=109 11%	N=115 42%	N=104 44%		
Improvement of endoscopic appearance of the mucosa at Week 52[d]					
Total Population	N=198 13%	N=198 37%	N=197 46%	24%* (16.0, 32.5)	33%* (24.2, 41.0)
With Prior TNF Inhibitor Failure[b]	N=89 12%	N=83 30%	N=93 40%		
Without Prior TNF Inhibitor Failure[c]	N=109 14%	N=115 43%	N=104 51%		
Sustained corticosteroid-free remission at both Week 24 and Week 52 among patients in remission at baseline[e]					
Total Population	N=59 5%	N=65 35%	N=55 47%	30%* (17.4, 43.2)	42%* (27.9, 56.5)
With Prior TNF Inhibitor Failure[b]	N=21 5%	N=18 22%	N=18 39%		
Without Prior TNF Inhibitor Failure[c]	N=38 5%	N=47 40%	N=37 51%		

* p-value <0.0001.
CI = Confidence interval; N = number of patients in the analysis set; TNF = tumour necrosis factor.
[a] Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.
[b] Prior TNF inhibitor failure was defined in this program as inadequate response, loss of response, or intolerance to TNF inhibitor therapy.
[c] Patients in this group had failed one or more conventional therapies (corticosteroid, azathioprine, 6-mercaptopurine) but did not have history of prior failure of TNF inhibitor therapy.
[d] 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).
[e] 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.

The proportion of patients in both XELJANZ groups who had treatment failure was lower compared to placebo at each time point as early as Week 8, the first time point where treatment failure was assessed.

Other health-related outcomes

XELJANZ 10 mg twice daily demonstrated greater improvement from baseline compared to placebo in physical component summary (PCS) and mental component summary (MCS) scores, and in all 8 domains of the SF-36 in the induction studies (OCTAVE Induction 1, OCTAVE Induction 2).

XELJANZ 10 mg twice daily demonstrated greater improvement from baseline compared to placebo in the total and all 4 domain scores of the Inflammatory Bowel Disease Questionnaire (IBDQ) at Week 8 in the induction studies (OCTAVE Induction 1, OCTAVE Induction 2).

Improvements were also observed in the EuroQoL 5-Dimension (EQ-5D) and various domains of the Work Productivity and Activity Impairment (WPAI-UC) questionnaire in the induction studies compared to placebo.

In general, improvements in quality of life measures were larger in patients given XELJANZ than in those given placebo in the maintenance study (OCTAVE Sustain).

Open-label extension study (OCTAVE Open)

Patients who did not achieve clinical response in 1 of the induction studies (OCTAVE Induction 1 or OCTAVE Induction 2) after 8 weeks of XEJLANZ 10 mg twice daily were allowed to enter an open-label extension study (OCTAVE Open). After an additional 8 weeks of XEJLANZ 10 mg twice daily in OCTAVE Open, 53% (154/293) patients achieved clinical response and 14% (42/293) patients achieved remission.

Patients who achieved clinical response in either of the induction studies (OCTAVE Induction 1 or OCTAVE Induction 2) with XELJANZ 10 mg twice daily but subsequently experienced treatment failure after either their dose was reduced to XELJANZ 5 mg twice daily or following treatment interruption in OCTAVE Sustain (i.e., were randomised to placebo), had their dose increased back to XELJANZ 10 mg twice daily in OCTAVE Open. After 8 weeks on XELJANZ 10 mg twice daily in OCTAVE Open, 38% of those patients who had experienced treatment failure in OCTAVE Sustain achieved remission; 35% (20/58) previously on XELJANZ 5 mg twice daily, and 40% (40/99) patients with previous dose interruption. At Month 12 in OCTAVE Open, 52% (25/48) and 45% (37/83) of these patients achieved remission, respectively.

Furthermore, at Month 12 of Study OCTAVE Open, 74% (48/65) of patients who achieved remission at the end of Study OCTAVE Sustain on either XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily remained in remission while receiving XELJANZ 5 mg twice daily.

5.2 Pharmacokinetic Properties

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

Absorption

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

Distribution

After intravenous administration, the volume of distribution is 87 L. Approximately 40% of circulating tofacitinib is bound to plasma proteins. Tofacitinib binds predominantly to albumin and does not appear to bind to a1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

Metabolism and Excretion

Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged drug, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of tofacitinib is attributed to the parent molecule. In vitro, tofacitinib is a substrate for multidrug resistance (MDR) 1, but not for breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1/1B3, or organic cationic transporter (OCT) 1/2, and is not an inhibitor of MDR1, OATP1B1/1B3, OCT2, organic anion transporter (OAT) 1/3, or multidrug resistance-associated protein (MRP) at clinically meaningful concentrations.

Special Populations

Pharmacokinetics in Elderly (>65 years) patients, Gender, Race

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

Results from population PK analysis in patients with active PsA or moderate to severe UC were consistent with those in patients with RA.

Children and Adolescents

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

Renal Impairment

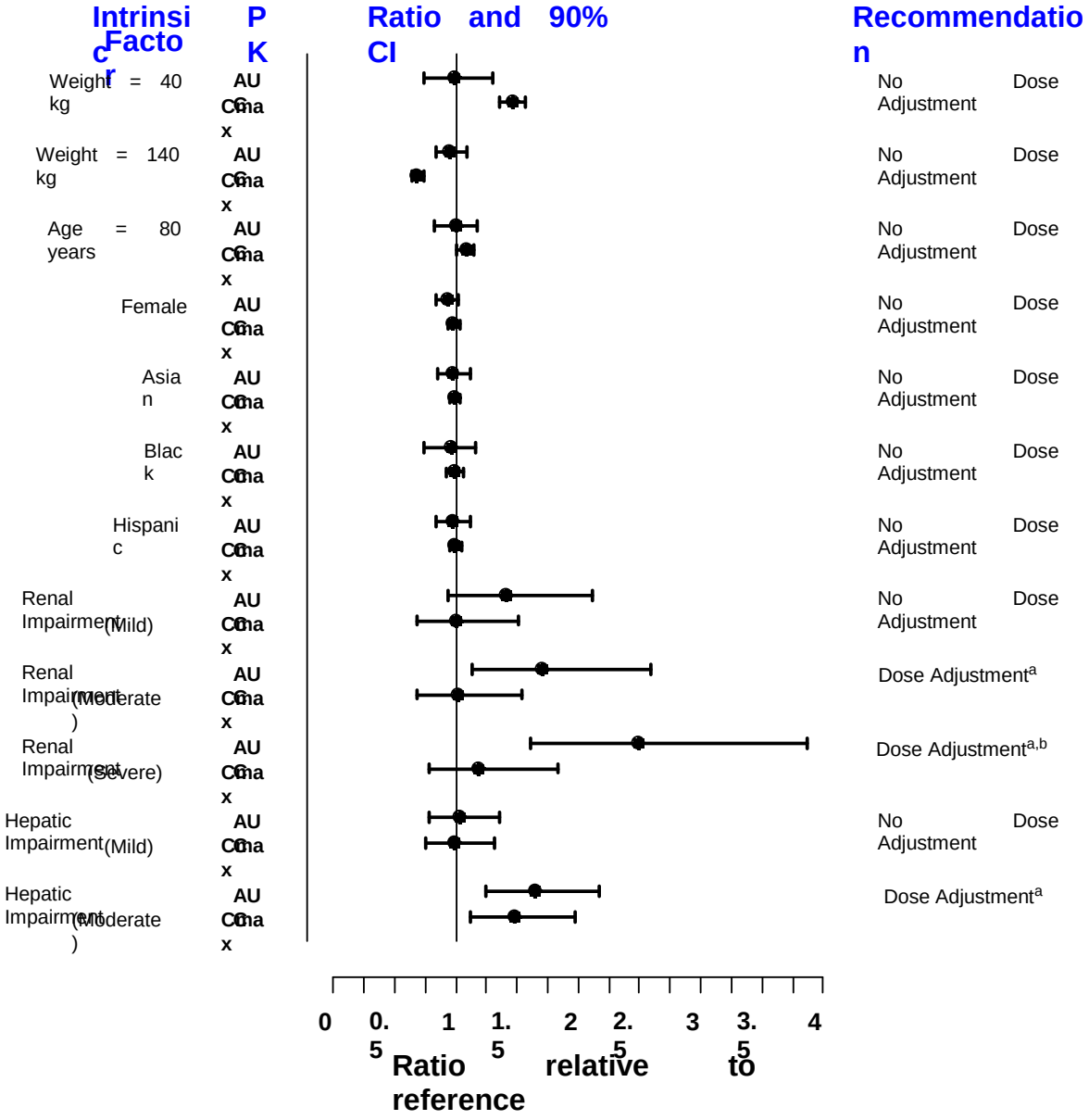
In a clinical study, subjects with renal impairment with a creatinine clearance of 51-80 mL/min, 30-50 mL/min and <30 mL/min (estimated GFR (Cockcroft–Gault formula)) had 37%, 43% and 123% higher AUC, respectively, compared with healthy subjects (see Section 4.2 Dose and Method of Administration). In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

Hepatic Impairment

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

The impact of intrinsic factors on tofacitinib pharmacokinetics is summarised in Figure 4 with dosage adjustment recommendations. Modifications required for special populations are described in Section 4.2 Dose and Method of Administration.

Figure 4: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics



Abbreviations: AUC=total area under the concentration time curve; Cmax= maximum plasma concentration; 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 or hepatic function.

[a] In rheumatoid arthritis and psoriatic arthritis patients the recommended dose is XELJANZ 5 mg once daily. In ulcerative colitis patients the recommended dose is half the total daily dose indicated for patients with normal renal and hepatic function; when the indicated dose in the presence of normal renal and hepatic function is XELJANZ 10 mg twice daily the recommended dose is XELJANZ 5 mg twice daily, and when the indicated

dose in the presence of normal renal and hepatic function is XELJANZ 5 mg twice daily the recommended dose is XELJANZ 5 mg once daily.
[b] Supplemental doses are not necessary in patients after dialysis.

5.3 Preclinical Safety Data

Genotoxicity

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

Carcinogenicity

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib was not carcinogenic in mice up to a high dose of 200 mg/kg/day (unbound drug AUC of ~38 times or ~19 times the human AUC at 5 mg or 10 mg twice daily). Benign Leydig cell tumours were observed in rats: benign Leydig cell tumours in rats are not associated with a risk of Leydig cell tumours in humans. Hibernomas (malignancy of brown adipose tissue) were observed in female rats at doses ≥30 mg/kg/day (unbound drug AUC of ~83 times or ~41 times the human AUC at 5 mg or 10 mg twice daily). Benign thymomas were observed in female rats dosed only at the 100 reduced to 75 mg/kg/day dose (unbound drug AUC of ~187 times or ~94 times the human AUC at 5 mg or 10 mg twice daily).

Lymphoma was observed in 3 of 8 adult and 0 of 14 juvenile monkeys dosed with tofacitinib at 5 mg/kg twice daily. The NOAEL for the lymphomas was 1 mg/kg twice daily. The unbound AUC at 1 mg/kg twice daily was 341 ng•h/mL, which is approximately half of the unbound AUC at 10 mg twice daily and similar to the unbound AUC at 5 mg twice daily in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:
microcrystalline cellulose
lactose monohydrate
croscarmellose sodium
magnesium stearate

Film coat:
hypromellose
titanium dioxide
lactose monohydrate
macrogol 3350
triacetin
indigo carmine aluminium lake (10 mg strength only)
brilliant blue FCF aluminium lake (10 mg strength only)

6.2 Incompatabilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Nature and Contents of Container

XELJANZ 5 mg

HDPE bottles with desiccant and child-resistant caps containing 60 or 180 film-coated tablets.

Aluminium/PVC-backed Aluminium blisters containing 14 or 56 film-coated tablets.

Not all pack sizes may be marketed.

XELJANZ 10 mg

Aluminium/PVC-backed Aluminium blisters containing 14 or 56 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

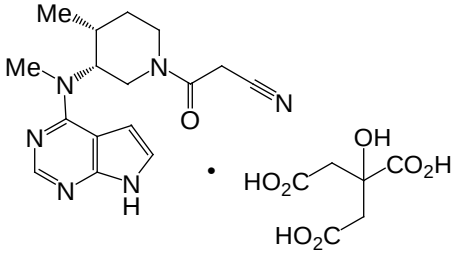
6.7 Physicochemical Properties

Chemical name: (3*R*,4*R*)-4-methyl-3-(methyl-7*H*-pyrrolo [2,3-*d*]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate

Molecular weight: 504.5 (312.4 for tofacitinib free base)

Molecular formula: $C_{16}H_{20}N_6O \bullet C_6H_8O_7$

Chemical structure



CAS number

540737-29-9 (citrate salt); 477600-75-2 (free base)

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

05 February 2015

10 DATE OF REVISION

19 February 2019

Ò Registered trademark

Summary table of changes

Section changed	Summary of new information
2	Addition of new 10 mg strength tablet details
3	Addition of new 10 mg strength tablet details
4.1	Ulcerative colitis (UC) indication added
4.2	Re-location of text from Section 4.1 regarding therapy with Xeljanz (initiation by a specialist physician with expertise in the management of conditions for which XELJANZ is indicated); Dosage instructions added for UC indication; Revision to dosage adjustments in neutropenia, renal impairment, hepatic impairment and interactions with other medicines.
4.4	Information updated to cover UC data (including 10 mg strength); use in hepatic impairment, use in renal impairment, effects on laboratory tests (neutrophils).
4.5	Update to Figure 1 (Impact of Other Medicines on the Pharmacokinetics of Tofacitinib); Information updated with regard to *in vitro* studies under 'Potential for Tofacitinib to Influence the Pharmacokinetics of Other Medicines' and to

	cover UC data under 'Combination with Other Therapies'.
4.6	Exposure margins updated to reflect new 10 mg strength under 'Effects on fertility' and 'Use in pregnancy'.
4.8	Information updated to include UC data; update to adverse drug reaction (ADR) frequencies
5.1	Information updated to include UC data with regard to clinical trials.
5.2	Information updated with regard to 'Metabolism and Excretion', 'Pharmacokinetics in Elderly (>65 years) patients, Gender, Race' and 'Renal Impairment'.
5.3	Exposure margins updated to reflect new 10 mg strength under 'Carcinogenicity'
6	Information updated to include new 10 mg strength.