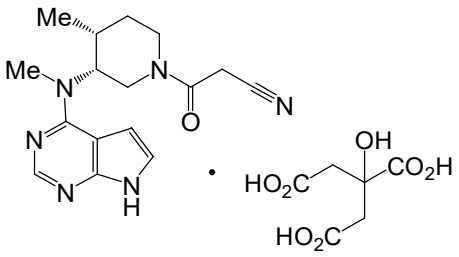
1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 5 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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



Excipients with known effect

Each 5 mg tablet also contains 62.567 mg lactose monohydrate.

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

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Rheumatoid Arthritis

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

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

Psoriatic Arthritis

XELJANZ (tofacitinib) in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy (see Section 5.1 Pharmacodynamic properties).

Ulcerative Colitis

XELJANZ (tofacitinib) 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 biologic agent (see Section 5.1 Pharmacodynamic properties).

4.2. Posology and method of administration

XELJANZ has not been studied and its use should be avoided in combination with tumor necrosis factor (TNF) antagonists, 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 potent immunosuppressants, such as azathioprine, cyclosporine, and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

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

Posology

Rheumatoid Arthritis

The recommended posology is 5 mg administered twice daily in combination with methotrexate.

Monotherapy may be considered in cases of intolerance to methotrexate.

Psoriatic Arthritis

The recommended dose is 5 mg administered twice daily, which should not be exceeded.

Ulcerative Colitis

Induction treatment

The recommended dose is 10 mg given orally twice daily for induction for 8 weeks.

For patients who do not achieve adequate therapeutic benefit by Week 8, 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. XELJANZ induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by Week 16.

Maintenance treatment

The recommended dose for maintenance treatment is XELJANZ 5 mg given orally twice daily.

XELJANZ 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known venous thromboembolism (VTE) risk factors, unless there is no suitable alternative treatment available (see Sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

For patients with UC who are not at increased risk for VTE (see Section 4.4 Special warnings and precautions for use), XELJANZ 10 mg orally twice daily may be considered if the patient experiences a decrease in response on XELJANZ 5 mg twice daily and failed to respond to alternative treatment options for ulcerative colitis such as tumor necrosis factor inhibitor (TNF inhibitor) treatment. XELJANZ 10 mg twice daily for maintenance treatment should be used for the shortest duration possible. The lowest effective dose needed to maintain response should be used.

In patients who have responded to treatment with XELJANZ, 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, re-induction 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).

Method of Administration

XELJANZ is given orally with or without food.

Dose Adjustments Due to Laboratory Abnormalities (see Section 4.4 Special warnings and precautions for use)

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

It is recommended that XELJANZ not be initiated in patients with a lymphocyte count less than 500 cells/mm^3.

Table 1: Dose Adjustments for Lymphopenia

Low Lymphocyte Count (see Section 4.4 Special warnings and precautions for use)	
Lab Value (cells/mm^3)	**Recommendation**
Lymphocyte count ≥500	Maintain dose.
Lymphocyte count <500 (Confirmed by repeat testing)	Discontinue XELJANZ.

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

Table 2: Dose Adjustments for Neutropenia

Low Absolute Neutrophil Count (ANC) (see Section 4.4 Special warnings and precautions for use)	
Lab Value (cells/mm^3)	**Recommendation**
ANC >1000	Maintain dose.
ANC 500-1000	For persistent decreases in this range, interrupt dosing until ANC is >1000. For patients receiving XELJANZ 5 mg twice daily, interrupt XELJANZ dosing. When ANC is >1000, resume XELJANZ 5 mg twice daily. For patients receiving XELJANZ 10 mg twice daily, reduce dose to XELJANZ 5 mg twice daily. When ANC is >1000, increase to XELJANZ 10 mg twice daily based on clinical response.
ANC <500 (Confirmed by repeat testing)	Discontinue XELJANZ.

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

Table 3: Dose Adjustments for Anemia

Low Hemoglobin Value (see Section 4.4 Special warnings and precautions for use)	
Lab Value (g/dL)	**Recommendation**
≤2 g/dL decrease and ≥9.0 g/dL	Maintain dose.
>2 g/dL decrease or less than 8.0 g/dL (Confirmed by repeat testing)	Interrupt the administration of XELJANZ until hemoglobin values have normalized.

Special Populations

Renal Impairment

If XELJANZ dose is 5 mg twice daily, the recommended dose in patients with severe renal impairment is XELJANZ 5 mg once daily (see Sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties). Specific recommendations for each indication are provided below.

Rheumatoid Arthritis

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

Psoriatic Arthritis

No dose adjustment is required in patients with mild renal impairment. XELJANZ dosage should be reduced to 5 mg once daily in patients with moderate or severe renal impairment

(including but not limited to those undergoing hemodialysis) (see Section 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Ulcerative Colitis

No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment (including but not limited to those undergoing hemodialysis), the recommended XELJANZ dose is 5 mg once daily if the dose in the presence of normal renal function is 5 mg twice daily (see Sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

In patients with severe renal impairment (including but not limited to those undergoing hemodialysis), the recommended XELJANZ dose is 5 mg twice daily if the dose in the presence of normal renal function is 10 mg twice daily (see Sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment. If XELJANZ dose is 5 mg twice daily, the recommended dose in patients with moderate hepatic impairment, is XELJANZ 5 mg once daily.

Rheumatoid Arthritis

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

Psoriatic Arthritis

No dose adjustment is required in patients with mild hepatic impairment. XELJANZ should not be used in patients with severe hepatic impairment. The recommended XELJANZ dose is 5 mg once daily in patients with moderate hepatic impairment (see Sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Ulcerative Colitis

No dose adjustment is required in patients with mild hepatic impairment. XELJANZ should not be used in patients with severe hepatic impairment. In patients with moderate hepatic impairment, the recommended XELJANZ dose is 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily, and the recommended dose is 5 mg once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily.

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

For indications with a maximum recommended dose of XELJANZ 5 mg twice daily in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole) or one or more

concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole), the recommended dose is XELJANZ 5 mg once daily. Specific recommendations for each indication are provided below.

Rheumatoid Arthritis

XELJANZ dosage should be reduced to 5 mg once daily in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole). XELJANZ dosage should be reduced to 5 mg once daily in patients receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

Psoriatic Arthritis

XELJANZ dosage should be reduced to 5 mg once daily in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole). XELJANZ dosage should be reduced to 5 mg once daily in patients receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

Ulcerative Colitis

In patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole) or one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole), the XELJANZ dose should be reduced to 5 mg twice daily if the patient is taking 10 mg twice daily, and the XELJANZ dose should be reduced to 5 mg once daily if the patient is taking 5 mg twice daily.

Patients Receiving Inducers of Cytochrome P450 (CYP3A4)

Co-administration of XELJANZ with potent CYP inducers (e.g., rifampin) may result in loss of or reduced clinical response (see Section 4.5 Interaction with other medicinal products and other forms of interaction). Co-administration of potent inducers of CYP3A4 with XELJANZ is not recommended.

Elderly Patients (≥65 years)

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

Pediatric

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

4.3. Contraindications

None.

4.4. Special warnings and precautions for use

Serious Infections

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

In one large randomized post-authorization safety study (PASS) in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, a dose dependent increase in serious infections was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1 Pharmacodynamic properties). Some of these serious infections resulted in death. Opportunistic infections were also reported in the study.

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

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

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes (see Section 4.8 Undesirable effects). Caution is also recommended in patients with a history of chronic lung disease as they may be more prone to infections. Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with tofacitinib, a Janus-kinase (JAK) inhibitor, in clinical trials and in the post-marketing setting although the role of JAK inhibition in these events is not known.

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

Tuberculosis

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

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

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

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with tofacitinib. In one large randomized post-authorization safety study (PASS) in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, an increase in herpes zoster events was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1 Pharmacodynamic properties). Post-marketing cases of hepatitis B reactivation have been reported in patients treated with tofacitinib. 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.

The risk of herpes zoster appears to be higher in Japanese and Korean patients treated with tofacitinib.

The incidence of herpes zoster appears to be increased in patients treated with tofacitinib 10 mg twice daily.

Venous Thromboembolism

Venous thromboembolism (VTE) has been observed in patients taking tofacitinib in clinical trials and post-marketing reporting (see Table 4 and Table 5 in Section 4.8 Undesirable effects). In one large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, patients were treated with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily or a TNF inhibitor. A dose dependent increase in pulmonary embolism (PE) events was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1 Pharmacodynamic properties). Many of these PE events were serious and some resulted in death. PE events were reported more frequently in this

study in patients taking tofacitinib relative to other studies across the tofacitinib program (see Sections 4.8 Undesirable effects and 5.1 Pharmacodynamic properties).

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

Assess patients for VTE risk factors before starting treatment and periodically during treatment. Use XELJANZ with caution in patients 65 years of age and older and in patients in whom VTE risk factors are identified (e.g., history of thrombosis). Urgently evaluate patients with signs and symptoms of VTE. Discontinue XELJANZ while evaluating suspected VTE, regardless of dose or indication.

Major Adverse Cardiovascular Events (Including Myocardial Infarction)

In one large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, patients were treated with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily or a TNF inhibitor. Major adverse cardiovascular events (MACE), including events of myocardial infarction, were observed in all three treatment groups in this study. An increase in non-fatal myocardial infarctions was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1 Pharmacodynamic properties). MACE, including events of myocardial infarction, were more common in patients 65 years of age and older, in patients who were current or past, long-time smokers, and in patients with a history of atherosclerotic cardiovascular disease (ASCVD). Caution should be used in treating patients 65 years of age and older, patients who are current or past, long-time smokers, and patients with other cardiovascular risk factors (e.g., history of ASCVD). In patients with these risk factors, an individualized benefit-risk assessment should be completed prior to a decision on treatment initiation or continuation (see Section 5.1 Pharmacodynamic properties).

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

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

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

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

Lung cancers have been observed in patients treated with tofacitinib. Lung cancers were also observed in patients treated with tofacitinib in a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor; an increase was observed in patients treated with tofacitinib 10 mg twice daily compared with TNF inhibitor (see Section 5.1 Pharmacodynamic properties). Of the 30 lung cancers reported in the study in patients taking tofacitinib, all but 2 were in patients who were current or past smokers. Patients with rheumatoid arthritis may be at higher risk than the general population for the development of lung cancer. The role of XELJANZ in the development of lung cancer is uncertain.

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

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

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

Rheumatoid Arthritis

In the 5 controlled Phase 3 clinical studies in rheumatoid arthritis patients, 21 malignancies (excluding NMSC) including 2 lymphomas were diagnosed in 21 patients receiving tofacitinib/tofacitinib plus DMARD, compared to 0 malignancies (excluding NMSC) in patients in the placebo/placebo plus DMARD and 2 in 2 patients in the adalimumab group. 3030 patients (2679 patient-years of observation) were treated with tofacitinib 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 0.78 and 0.075 events per 100 patient-years, respectively, in the tofacitinib groups.

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

In a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, an increase in malignancies (excluding NMSC) was observed in patients treated with tofacitinib compared with TNF inhibitor (see Section 5.1 Pharmacodynamic properties). Malignancies (excluding NMSC) were more common in

patients 65 years of age and older and in patients who were current or past, long-time smokers.

Psoriatic Arthritis

In 2 controlled Phase 3 clinical trials in patients with active psoriatic arthritis, there were 3 malignancies (excluding NMSC) in 474 patients (298 patient-years of observation) receiving tofacitinib 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 tofacitinib 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

In the placebo-controlled induction and maintenance studies for ulcerative colitis, there were no malignancies (excluding NMSC) in any tofacitinib group. In the entire tofacitinib treatment experience for ulcerative colitis, malignancies (excluding NMSC) have been reported with an overall incidence rate of 0.5 events per 100 patient-years.

In Cohort 3 P2P3LTE Tofacitinib study, the IRs (95% CI) for PD tofacitinib 5 mg and PD tofacitinib 10 mg for all malignancies (excluding NMSC) were 0.00 (0.00, 1.00) and 0.62 (0.27, 1.22) patients with events per 100 PYs respectively.

<u>Non-melanoma Skin Cancer</u>

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with tofacitinib. NMSCs were also reported in a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor. In this study, an increase in overall NMSCs, including cutaneous squamous cell carcinomas was observed in patients treated with tofacitinib compared to TNF inhibitor (see Section 5.1 Pharmacodynamic properties). As there is a higher incidence of NMSC in the elderly and in patients with a prior history of NMSC, caution should be used when treating these types of patients. The risk of NMSC may be higher in patients treated with tofacitinib 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

<u>Gastrointestinal Perforations</u>

Events of gastrointestinal perforation have been reported in clinical trials including a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (see Section 5.1 Pharmacodynamic properties). The role of JAK inhibition in these events is not known. In the rheumatoid arthritis clinical trials, the incidence rate of gastrointestinal perforation across all studies (Phase 1, Phase 2, Phase 3

(excluding A3921069) and long-term extension) for all treatments groups all doses was 0.12 events per 100 patient-years with tofacitinib therapy. Events were primarily reported as diverticular perforation, peritonitis, abdominal abscess and appendicitis. Rheumatoid arthritis patients who developed gastrointestinal perforations were taking concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. The relative contribution of these concomitant medications vs. tofacitinib to the development of gastrointestinal perforations is not known. The incidence rate in the psoriatic arthritis clinical trials (Phase 3 and long-term extension) was 0.08 patients with events per 100 patient-years with tofacitinib therapy.

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

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

Fractures

Fractures have been observed in patients treated with XELJANZ in clinical studies and the post-marketing setting.

In controlled Phase 3 clinical studies in RA patients, during the 0 to 3 months exposure, the incidence rates for fractures for XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and placebo were 2.11, 2.56 and 4.43 patients with events per 100 PYs, respectively.

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

Caution should be used in patients with known risk factors for fractures such as elderly patients, female patients and patients with corticosteroid use.

Hypersensitivity

Reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients receiving tofacitinib. 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 XELJANZ while evaluating the potential cause or causes of the reaction.

Laboratory Parameters

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

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

Neutrophils: Treatment with XELJANZ was associated with an increased incidence of neutropenia (<2000 cells/mm^3) compared to placebo. It is not recommended to initiate XELJANZ treatment in patients with a low neutrophil count (i.e., ANC <1000 cells/mm^3). For patients taking XELJANZ 10 mg twice daily who develop a persistent ANC of 500-1000 cells/mm3, reduce XELJANZ dose to 5 mg twice daily until ANC is >1000 cells/mm^3. For patients taking XELJANZ 5 mg twice daily who develop a persistent ANC of 500-1000 cells/mm^3, interrupt dosing until ANC is >1000 cells/mm^3. In patients who develop a confirmed absolute neutrophil count <500 cells/mm^3 treatment with XELJANZ is not recommended. Neutrophils should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter (see Sections 4.2 Posology and method of administration and 4.8 Undesirable effects).

Hemoglobin: It is not recommended to initiate XELJANZ treatment in patients with low hemoglobin values (i.e., <9 g/dL). Treatment with XELJANZ should be interrupted in patients who develop hemoglobin levels <8 g/dL or whose hemoglobin level drops >2 g/dL on treatment. Hemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter (see Sections 4.2 Posology and method of administration and 4.8 Undesirable effects).

Liver Enzymes: Treatment with tofacitinib was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) 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, the administration of XELJANZ should be interrupted until this diagnosis has been excluded.

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

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

<u>Hypoglycemia in Patients Treated for Diabetes</u>

There have been reports of hypoglycemia following initiation of XELJANZ in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycemia occurs.

Vaccinations

No data are available on the secondary transmission of infection by live vaccines to patients receiving tofacitinib. It is recommended that live vaccines not be given concurrently with XELJANZ. It is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating XELJANZ therapy. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunomodulatory agents. Consistent with these guidelines, if live zoster vaccine is administered, it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus. Vaccination should occur at least 2 weeks but preferably 4 weeks before initiating immunomodulatory agents such as tofacitinib.

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

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

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

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

antibody responses to the vaccine approximately 6 weeks post-vaccination, but not at 2 weeks post-vaccination, as expected for a primary infection.

Patients with Renal Impairment

No dose adjustment is required in patients with mild renal impairment. If XELJANZ dose is 5 mg twice daily, the recommended dose in patients with severe renal impairment is XELJANZ 5 mg once daily. For specific dose adjustment recommendations for each indication, see Section 4.2 Posology and method of administration.

In clinical trials, tofacitinib was not evaluated in patients with baseline creatinine clearance values (estimated by Cockcroft-Gault equation) <40 mL/min (see Sections 4.2 Posology and method of administration and 5.2 Pharmacokinetic properties).

Patients with Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment. If XELJANZ dose is 5 mg twice daily, the recommended dose in patients with moderate hepatic impairment, is XELJANZ 5 mg once daily. For specific dose adjustment recommendations for each indication, see Section 4.2 Posology and method of administration.

XELJANZ should not be used in patients with severe hepatic impairment (see Section 4.2 Posology and method of administration). In clinical trials, tofacitinib was not evaluated in patients with severe hepatic impairment, or in patients with positive HBV or HCV serology.

Combination with Other Therapies

Rheumatoid Arthritis

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

Psoriatic Arthritis

XELJANZ has not been studied and its use should be avoided in patients with active psoriatic arthritis in combination with biological DMARDs such as TNF antagonists, IL-17 antagonists, and IL-12/IL-23 antagonists, and potent immunosuppressants, such as azathioprine and cyclosporine because of the possibility of increased immunosuppression and increased risk of infection.

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

Ulcerative Colitis

XELJANZ has not been studied and its use should be avoided in patients with ulcerative colitis in combination with biological agents such as TNF antagonists and vedolizumab,

and/or potent immunosuppressants such as azathioprine, 6-mercaptopurine, tacrolimus, and cyclosporine because of the possibility of increased immunosuppression and increased risk of infection.

4.5. Interaction with other medicinal products and other forms of interaction

Interactions Affecting the Use of XELJANZ

Since tofacitinib is metabolized by CYP3A4, interaction with drugs that inhibit or induce CYP3A4 is likely. Tofacitinib exposure is increased when co-administered with potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) or when administration of one or more concomitant medications results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole) (see Section 4.2 Posology and method of administration).

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

Concomitant administration with methotrexate (15-25 mg MTX once weekly) had no effect on the PK of tofacitinib. Co-administration of ketoconazole, a strong CYP3A4 inhibitor, with a single dose of tofacitinib increased the AUC and C_{max} by 103% and 16%, respectively. Co-administration of fluconazole, a moderate inhibitor of CYP3A4 and a strong inhibitor of CYP2C19, increased the AUC and C_{max} of tofacitinib by 79% and 27%, respectively. Co-administration of tacrolimus (Tac), a mild inhibitor of CYP3A4, increased the AUC of tofacitinib by 21% and decreased the C_{max} of tofacitinib by 9%. Co-administration of cyclosporine (CsA), a moderate inhibitor of CYP3A4, increased the AUC of tofacitinib by 73% and decreased C_{max} of tofacitinib by 17%. The combined use of multiple-dose tofacitinib with these potent immunosuppressives has not been studied in patients with rheumatoid arthritis or psoriatic arthritis. Co-administration of rifampin, a strong CYP3A4 inducer, decreased the AUC and C_{max} of tofacitinib by 84% and 74%, respectively (see Section 4.2 Posology and method of administration).

Potential for XELJANZ to Influence the PK of Other Drugs

In vitro studies indicate that tofacitinib does not significantly inhibit or induce the activity of the major human drug metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations exceeding 80 times the steady-state total C_{max} at 5 mg twice daily doses in rheumatoid arthritis patients and psoriatic arthritis patients. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the PK of midazolam, a highly sensitive CYP3A4 substrate, when co-administered with tofacitinib.

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

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

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

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

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

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

Pediatric Population

Studies have only been performed in adults.

4.6. Fertility, pregnancy and lactation

There are no adequate and well-controlled studies on the use of XELJANZ in pregnant women. Tofacitinib has been shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility, parturition, and peri/post-natal development (see Section 5.3 Non-clinical safety data). XELJANZ should not be used during pregnancy unless clearly necessary.

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

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

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Rheumatoid Arthritis

The following data includes 5 double-blind, controlled, multicenter studies of varying durations from 6-24 months (Studies I-V, see Section 5.1 Pharmacodynamic properties). In these studies, 2430 patients were randomized and treated to doses of tofacitinib 5 mg twice daily (243 patients) or 10 mg twice daily (245 patients) monotherapy and tofacitinib 5 mg twice daily (973 patients) or 10 mg twice daily (969 patients) in combination with DMARDs (including methotrexate).

All patients in these studies had moderate to severe rheumatoid arthritis. The study tofacitinib population had a mean age of 52.7 years and 84.1% were female.

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

A total of 5305 patients (Phase 1, 2, 3 (excluding A3921069), and long-term extension studies) were treated with any dose of tofacitinib with a mean duration of 3.16 years, with 16785.8 patient-years of accumulated total drug exposure based on more than 8 years of continuous exposure to tofacitinib.

Safety information is also included for one large (N=4362), randomized post-authorization safety study (PASS) in RA patients who were 50 years or older with at least one additional cardiovascular risk factor (CV risk factors defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g., nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations), and were on a stable background dose of methotrexate. The majority (more than 90%) of tofacitinib patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively.

Patients were randomized to open-label tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, or a TNF inhibitor (TNF inhibitor was either etanercept 50 mg once weekly or adalimumab 40 mg every other week) in a 1:1:1 ratio. The co-primary endpoints are adjudicated malignancy (excluding NMSC) and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessment of endpoints are blinded. The study is an event-powered study that also requires at least 1500 patients to be followed for 3 years. The study treatment of tofacitinib 10 mg twice daily has been stopped and the patients were switched to 5 mg twice daily because of a dose dependent signal of PE.

Psoriatic Arthritis

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

Study PsA-I (OPAL BROADEN) 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 (OPAL BROADEN) included a 3-month placebo-controlled period and also included adalimumab 40 mg subcutaneously once every 2 weeks for 12 months. Study PsA-II (OPAL BEYOND) had a duration of 6 months and included 394 patients who had an inadequate response to at least one approved TNFi. Study PsA-II (OPAL BEYOND) included a 3-month placebo-controlled period. All patients in the clinical trials were required to receive treatment with a stable dose of a csDMARD [the majority received methotrexate (78.2%)]. In the Phase 3 clinical trials, patients were randomized and treated with tofacitinib 5 mg twice daily (238 patients) or tofacitinib 10 mg twice daily (236 patients). The study population randomized and treated with tofacitinib (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 psoriatic arthritis who originally participated in either of the 2 double-blind, controlled clinical trials. Patients who participated in this open-label clinical trial were initially treated with tofacitinib 5 mg twice daily. Starting at Month 1, escalation to tofacitinib 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 tofacitinib doses of 5 mg twice daily or 10 mg twice daily in psoriatic arthritis 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 randomized, double-blind, placebo-controlled studies: 2 Phase 3 induction studies of identical design (OCTAVE Induction 1 and OCTAVE Induction 2), a Phase 3 maintenance study (OCTAVE Sustain), and 1 dose-ranging Phase 2 induction study (UC-V). Patients with moderately to severely active ulcerative colitis were enrolled in the Phase 2 and Phase 3 induction studies. In the induction studies, randomized patients received treatment with tofacitinib 10 mg twice daily (938 patients combined) or placebo (282 patients combined) for up to 8 weeks. Patients who completed either OCTAVE Induction 1 or OCTAVE Induction 2 and achieved clinical response entered OCTAVE Sustain. In OCTAVE Sustain, patients were re-randomized, such that 198 patients received tofacitinib 5 mg twice daily, 196 patients received tofacitinib 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 (OCTAVE Open).

<u>Clinical Trials Experience</u>

The most common category of serious adverse reactions in rheumatoid arthritis was serious infections (see Section 4.4 Special warnings and precautions for use).

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

Rheumatoid Arthritis

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

The proportion of patients who discontinued treatment due to any adverse reactions during first 3 months of the double-blind, placebo-controlled studies was 4.2% for patients taking tofacitinib and 3.2% for placebo-treated patients. The most common infections resulting in discontinuation of therapy were herpes zoster and pneumonia.

Psoriatic Arthritis

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

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

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

Ulcerative Colitis

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

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

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

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

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

Serious Infections

In the seven controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.5 events per 100 patient-years) who received placebo and 11 patients (1.7 events per 100 patient-years) who received tofacitinib 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 1.1 (-0.4, 2.5) events per 100 patient-years for the combined 5 mg twice daily and 10 mg twice daily tofacitinib group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, serious infections were reported in 34 patients (2.7 events per 100 patient-years) who received 5 mg twice daily of tofacitinib and 33 patients (2.7 events per 100 patient-years) who received 10 mg twice daily of tofacitinib. The rate difference between tofacitinib doses (and the corresponding 95% confidence interval) was -0.1 (-1.3, 1.2) events per 100 patient-years for 10 mg twice daily tofacitinib minus 5 mg twice daily tofacitinib.

The most common serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infection (see Section 4.4 Special warnings and precautions for use).

Tuberculosis

In the seven controlled trials, during the 0 to 3 months exposure, tuberculosis was not reported in patients who received placebo, 5 mg twice daily of tofacitinib, or 10 mg twice daily of tofacitinib.

In the seven controlled trials, during the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg twice daily of tofacitinib and 6 patients (0.5 events per 100 patient-years) who received 10 mg twice daily of tofacitinib. The rate difference between tofacitinib doses (and the corresponding 95% confidence interval) was 0.5 (0.1, 0.9) events per 100 patient-years for 10 mg twice daily tofacitinib minus 5 mg twice daily tofacitinib.

Cases of disseminated tuberculosis were also reported. The median tofacitinib exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days) (see Section 4.4 Special warnings and precautions for use).

Opportunistic Infections (Excluding Tuberculosis)

In the seven controlled trials, during the 0 to 3 months exposure, opportunistic infections were not reported in patients who received placebo, 5 mg twice daily of tofacitinib, or 10 mg twice daily of tofacitinib.

In the seven controlled trials, during the 0 to 12 months exposure, opportunistic infections were reported in 4 patients (0.3 events per 100 patient-years) who received 5 mg twice daily of tofacitinib and 4 patients (0.3 events per 100 patient-years) who received 10 mg twice daily of tofacitinib. The rate difference between tofacitinib doses (and the corresponding 95% confidence interval) was 0 (-0.5, 0.5) events per 100 patient-years for 10 mg twice daily tofacitinib minus 5 mg twice daily tofacitinib.

The median tofacitinib exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days) (see Section 4.4 Special warnings and precautions for use).

Malignancy

In the seven controlled trials, during the 0 to 3 months exposure, malignancies excluding NMSC were reported in 0 patients who received placebo and 2 patients (0.3 events per 100 patient-years) who received either tofacitinib 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 0.3 (-0.1, 0.7) events per 100 patient-years for the combined 5 mg and 10 mg twice daily tofacitinib group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, malignancies excluding NMSC were reported in 5 patients (0.4 events per 100 patient-years) who received 5 mg twice daily of tofacitinib and 7 patients (0.6 events per 100 patient-years) who received 10 mg twice daily of tofacitinib. The rate difference between tofacitinib doses (and the corresponding 95% confidence interval) was 0.2 (-0.4, 0.7) events per 100 patient-years for 10 mg twice daily tofacitinib minus 5 mg twice daily tofacitinib. One of these malignancies was a case of lymphoma that occurred during the 0 to 12 month period in a patient treated with tofacitinib 10 mg twice daily.

The most common types of malignancy, including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma, and malignant melanoma (see Section 4.4 Special warnings and precautions for use).

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

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

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
Infections and infestations		Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Nasopharyngitis Pharyngitis	Tuberculosis Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection	Sepsis Tuberculosis of central nervous system[b] Meningitis cryptococcal[b] Urosepsis Disseminated tuberculosis

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
				Necrotizing fasciitis[b] Bacteremia[b] Staphylococcal bacteremia[b] *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal[b] Pneumonia bacterial Encephalitis[b] Atypical mycobacterial infection[b] *Mycobacterium avium* complex infection[b] Cytomegalovirus infection Arthritis bacterial[c]
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Non-melanoma skin cancers[d]	
Blood and lymphatic system disorders		Anemia	Leukopenia Lymphopenia Neutropenia	
Immune system disorders			Drug hypersensitivity[e]	
Metabolism and nutrition disorders		Hyperlipidemia	Dyslipidemia Dehydration	
Psychiatric disorders			Insomnia	
Nervous system disorders		Headache	Paresthesia	
Vascular disorders		Hypertension	Venous thromboembolism[f]	
Respiratory, thoracic and mediastinal disorders		Cough	Dyspnea Sinus congestion	
Gastrointestinal disorders		Abdominal pain Vomiting Diarrhea Nausea Gastritis Dyspepsia		
Hepatobiliary disorders			Hepatic steatosis	
Skin and subcutaneous tissue disorders		Rash Acne[g]	Erythema Pruritus	

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
Musculoskeletal and connective tissue disorders		Arthralgia	Musculoskeletal pain Joint swelling Tendonitis	
General disorders and administration site conditions		Pyrexia Edema peripheral Fatigue		
Investigations		Gamma-glutamyltransferase increased Blood cholesterol increased Weight increased Blood creatine phosphokinase increased	Hepatic enzyme increased Transaminases increased Liver function test abnormal Blood creatinine increased Low density lipoprotein increased	
Injury, poisoning and procedural complications			Ligament sprain Muscle strain	

Abbreviations: ADR=adverse drug reaction; NMSC=non-melanoma skin cancers; PsA=psoriatic arthritis; PsO=psoriasis; PT=preferred term; RA=rheumatoid arthritis; UC=ulcerative colitis.
[a] The frequencies are based on pooled Phase 3 randomized clinical trial data across 4 indications RA, PsO, PsA, and UC (excluding Study A3921133).
[b] The adverse drug reactions have only been reported in open-label long-term extension studies; therefore the frequency of these adverse drug reactions in Phase 3 randomized trials was estimated.
[c] The frequency of arthritis bacterial is determined by combined frequencies for PTs of arthritis bacterial and arthritis infective.
[d] NMSC identified as ADR in 2013; NMSC is not a PT: the frequency is determined by combining frequencies for PTs of basal cell cancer and squamous cell cancer of the skin.
[e] Spontaneous reporting data (events such as angioedema and urticaria have been observed). Some events were also observed in clinical trials.
[f] Venous thromboembolism (e.g., pulmonary embolism, deep vein thrombosis, retinal venous thrombosis, and cerebral venous sinus thrombosis).
[g] Adverse Drug Reaction (ADR) identified post-marketing.

Table 5: Adverse Drug Reactions by SOC and CIOMS Frequency Categories for Tofacitinib (RA Program - A3921133)[d]

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000
Infections and infestations	Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Nasopharyngitis Pharyngitis Tuberculosis	Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection Sepsis Arthritis bacterial[a]	Urosepsis Disseminated tuberculosis *Pneumocystis jirovecii* pneumonia Pneumonia bacterial	Bacteraemia Pneumonia pneumococcal Cytomegalovirus infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Non-melanoma skin cancers[b]		

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000
Blood and lymphatic system disorders	Anemia Lymphopenia	Leukopenia Neutropenia		
Immune system disorders		Drug hypersensitivity		
Metabolism and nutrition disorders		Hyperlipidemia Dyslipidemia	Dehydration	
Psychiatric disorders		Insomnia		
Nervous system disorders	Headache	Paresthesia		
Vascular disorders	Hypertension	Venous thromboembolism[c]		
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnea Sinus congestion		
Gastrointestinal disorders	Diarrhea Nausea	Abdominal pain Vomiting Gastritis Dyspepsia		
Hepatobiliary disorders		Hepatic steatosis		
Skin and subcutaneous tissue disorders		Rash Acne[e] Erythema Pruritus		
Musculoskeletal and connective tissue disorders	Arthralgia	Joint swelling Tendonitis	Musculoskeletal pain	
General disorders and administration site conditions	Edema peripheral	Pyrexia Fatigue		
Investigations		Blood cholesterol increased Weight increased Hepatic enzyme increased Transaminases increased	Gamma-glutamyltransferase increased Blood creatine phosphokinase increased Liver function test abnormal Blood creatinine increased Low density lipoprotein increased	
Injury, poisoning and procedural complications		Ligament sprain Muscle strain		

Abbreviations: ADR=adverse drug reaction; NMSC=non-melanoma skin cancers; PT=preferred term; RA=rheumatoid arthritis.
[a] The frequency of arthritis bacterial is determined by combined frequencies for PTs of arthritis bacterial and arthritis infective.
[b] NMSC identified as ADR in 2013; NMSC is not a PT: the frequency is determined by combining frequencies for PTs of basal cell cancer and squamous cell cancer of the skin.

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000
[c] Venous thromboembolism (e.g., pulmonary embolism, deep vein thrombosis, retinal venous thrombosis, and cerebral venous sinus thrombosis). [d] Table is based on incidence rates per 100 patient-years. [e] Adverse Drug Reaction (ADR) identified post-marketing.				

Overall Infections

Rheumatoid Arthritis

In the 6-month, controlled Phase 3 clinical study the rates of infections in the 5 mg twice daily (total 243 patients) and 10 mg twice daily (total 245 patients) tofacitinib monotherapy group were 16.5% (40 patients), and 19.2% (47 patients), respectively, compared to 18.9% (23 patients) in the placebo group (total 122 patients). In studies of 6-month, 12-month, or 24-month duration with background DMARDs, the rates of infections in the 5 mg twice daily (total 973 patients) and 10 mg twice daily (total 969 patients) tofacitinib plus DMARD group were 21.3% (207 patients) and 21.8% (211 patients), respectively, compared to 18.4% (103 patients) in the placebo plus DMARD group (total 559 patients).

The most commonly reported infections were upper respiratory tract infections and nasopharyngitis (4.1% and 3.4%, respectively).

The overall rate of infections with tofacitinib in the long-term safety all exposure population (total 4867 patients) was 46.1 patients with events per 100 patient-years (43.8 and 47.2 patients with events for 5 mg and 10 mg twice daily, respectively). For patients (total 1750) on monotherapy, the rates were 48.9 and 41.9 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively. For patients (total 3117) on background DMARDs, the rates were 41.0 and 50.3 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively.

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

Psoriatic Arthritis

In the controlled Phase 3 studies of up to 6-month and up to 12-month, the frequency of infections in the tofacitinib 5 mg twice daily (238 patients) and tofacitinib 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 tofacitinib 5 mg twice daily (238 patients), 28.8% for tofacitinib 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 tofacitinib in the long-term safety population for combined doses was 52.3 patients with events per 100 patient-years.

Ulcerative Colitis

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

Serious Infections

Rheumatoid Arthritis

In the 6-month, controlled clinical study, the rate of serious infections in the 5 mg twice daily tofacitinib monotherapy group was 0.85 patients with events per 100 patient-years. In the 10 mg twice daily tofacitinib monotherapy group, the rate was 3.5 patients with events per 100 patient-years, and the rate was 0 events per 100 patient-years for the placebo group.

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

In the long-term safety all exposure population comprised of Phase 2 and Phase 3 clinical trials and long-term extension studies, the overall rates of serious infections were 2.4 and 3.0 patients with events per 100 patient-years for 5 mg and 10 mg twice daily tofacitinib groups, respectively. The most common serious infections reported with tofacitinib included pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis, and diverticulitis. Cases of opportunistic infections have been reported (see Section 4.4 Special warnings and precautions for use).

Of the 3315 patients who enrolled in Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among tofacitinib-treated patients 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

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

Psoriatic Arthritis

In the 6-month and 12-month Phase 3 studies, the rate of serious infections in the tofacitinib 5 mg twice daily group was 1.30 patients with events per 100 patient-years. In the tofacitinib 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 tofacitinib-treated patients. The most common serious infection reported with tofacitinib was pneumonia.

Ulcerative Colitis

In the randomized 8-week Phase 2/3 induction studies, the proportion of patients with serious infections in patients treated with tofacitinib 10 mg twice daily was 0.9% (8 patients) compared with 0.0% in patients treated with placebo. In the randomized 52-week Phase 3 maintenance study, the incidence rates of serious infections in patients treated with tofacitinib 5 mg twice daily (1.35 events per 100 patient-year) and in patients treated with tofacitinib 10 mg twice daily (0.64 events per 100 patient-year) were not higher than that for placebo (1.94 events per 100 patient-year). The incidence rate of serious infections in the entire treatment experience with tofacitinib in patients with ulcerative colitis was 2.05 events per 100 patient-year. There was no apparent clustering into specific types of serious infections.

Viral Reactivation

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

Venous Thromboembolism

Rheumatoid Arthritis

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

Completed Rheumatoid Arthritis Studies

In the 4 to 12 week placebo period of randomized controlled studies of 4 weeks to 24 months duration, the IRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and placebo for PE were 0.00 (0.00, 0.57), 0.00 (0.00, 0.77), and 0.40 (0.01, 2.22) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.00 (0.00, 0.57), 0.21 (0.01, 1.16), and 0.40 (0.01, 2.22) patients with events per 100 PYs respectively.

In the full randomized period of controlled studies of 4 weeks to 24 months duration, the IRs (95% CI) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily for PE were 0.12 (0.02, 0.34) and 0.15 (0.03, 0.44) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.15 (0.04, 0.40) and 0.10 (0.01, 0.36) patients with events per 100 PYs respectively.

In the long term safety population that includes exposure during completed randomized controlled studies and open-label long-term extension studies, the IRs (95% CI) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily for PE were 0.12 (0.06, 0.22) and 0.13 (0.08, 0.21) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.17 (0.09, 0.27) and 0.15 (0.09, 0.22) patients with events per 100 PYs respectively.

Psoriatic Arthritis

In the 3 month placebo period of completed randomized controlled studies of 6 to 12 months duration, the IRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and placebo for PE were 0.00 (0.00, 6.75), 0.00 (0.00, 6.78), and 0.00 (0.00, 6.87) patients with events per 100 PYs respectively; the IRs (95% CI) for DVT were 0.00 (0.00, 6.75), 0.00 (0.00, 6.78), and 0.00 (0.00, 6.87) patients with events per 100 PYs respectively.

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

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

Ulcerative Colitis

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

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

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

Laboratory Tests

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

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

Rheumatoid Arthritis

Lymphocytes

In the controlled clinical studies, confirmed decreases in lymphocyte counts below 500 cells/mm^3 occurred in 0.26% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

In the long-term safety population, confirmed decreases in lymphocyte counts below 500 cells/mm^3 occurred in 1.3% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

Confirmed lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections (see Section 4.4 Special warnings and precautions for use).

Neutrophils

In the controlled clinical studies confirmed decreases in ANC below 1000 cells/mm^3 occurred in 0.08% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. There were no confirmed decreases in ANC below 500 cells/mm^3 observed in any treatment group. There was no clear relationship between neutropenia and the occurrence of serious infections.

In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical studies (see Section 4.4 Special warnings and precautions for use).

Liver Enzyme Tests

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

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

In the controlled portion of the Phase 3 studies on background DMARDs (0-3 months) (Studies II-V, see Section 5.1 Pharmacodynamic properties), ALT elevations >3x ULN were observed in 0.9%, 1.24% and 1.14% of patients receiving placebo, tofacitinib 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, tofacitinib 5 mg, and 10 mg twice daily, respectively.

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

Lipids

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

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

- Mean LDL cholesterol increased by 14% in the tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at Month 12, and increased by 14% in the tofacitinib 5 mg twice daily arm and 15% in the tofacitinib 10 mg twice daily arm at Month 24.
- Mean HDL cholesterol increased by 16% in the tofacitinib 5 mg twice daily arm and 18% in the tofacitinib 10 mg twice daily arm at Month 12, and increased by 18% in the tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at Month 24.
- Mean LDL cholesterol/HDL cholesterol ratios were essentially unchanged in tofacitinib-treated patients.
- Apolipoprotein B (ApoB)/ApoA1 ratios were essentially unchanged in tofacitinib-treated patients.

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

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 population, 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 tofacitinib treatment. The mean increase in serum creatinine was <0.1 mg/dL in the 12-month pooled safety analysis; however with increasing duration of exposure in the

long-term extensions, up to 2% of patients were discontinued from tofacitinib 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.

4.9. Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Mechanism of Action

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

Pharmacodynamic Effect

In patients with rheumatoid arthritis, treatment up to 6 months with 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+ natural

killer 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.

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

After treatment with tofacitinib in patients with rheumatoid arthritis, rapid decreases in serum C-reactive protein (CRP) were observed and maintained throughout dosing. Changes in CRP observed with tofacitinib 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 psoriatic arthritis, although reversibility was not assessed. Total serum immunoglobulins were not assessed in patients with active psoriatic arthritis.

Clinical Safety

In one large randomized open-label PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor and on a stable dose of methotrexate, patients were treated with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily or a TNF inhibitor. Notably, in February 2019, the dose of tofacitinib in the 10 mg twice daily arm of the study was reduced to 5 mg twice daily after it was determined that the frequency of pulmonary embolism was increased in the tofacitinib 10 mg twice daily treatment arm versus the TNF inhibitor. Additionally, all-cause mortality was increased in the tofacitinib 10 mg twice daily treatment arm versus the TNF inhibitor and tofacitinib 5 mg twice daily treatment arms. In the final study data, patients in the tofacitinib 10 mg twice daily treatment arm were analyzed in their originally randomized treatment group. Results from final safety data from the study for selected events follow below.

Mortality

The IRs (95% CI) for all-cause mortality for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.50 (0.33, 0.74), 0.80 (0.57, 1.09), 0.65 (0.50, 0.82), and 0.34 (0.20, 0.54) events per 100 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.49 (0.81, 2.74), 2.37 (1.34, 4.18), and 1.91 (1.12, 3.27), respectively.

The IRs (95% CI) for deaths associated with infection for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.08 (0.02, 0.20), 0.18 (0.08, 0.35), 0.13 (0.07, 0.22), and 0.06 (0.01, 0.17) events per 100 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.30 (0.29, 5.79), 3.10 (0.84, 11.45), and 2.17 (0.62, 7.62), respectively.

The IRs (95% CI) for deaths associated with cardiovascular events for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.25 (0.13, 0.43), 0.41 (0.25, 0.63), 0.33 (0.23, 0.46), and 0.20 (0.10, 0.36) events per 100 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.26 (0.55, 2.88), 2.05 (0.96, 4.39), and 1.65 (0.81, 3.34), respectively.

The IRs (95% CI) for deaths associated with malignancies for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.10 (0.03, 0.23), 0.00 (0.00, 0.08), 0.05 (0.02, 0.12), and 0.02 (0.00, 0.11) events per 100 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 4.88 (0.57, 41.74), 0 (0.00, Inf), and 2.53 (0.30, 21.64), respectively.

The IRs (95% CI) for deaths associated with other causes (excluding infections, cardiovascular events, malignancies) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.08 (0.02, 0.20), 0.21 (0.10, 0.38), 0.14 (0.08, 0.23), and 0.06 (0.01, 0.17) events per 100 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.30 (0.29, 5.81), 3.45 (0.95, 12.54), and 2.34 (0.67, 8.16), respectively.

Infections

The IRs (95% CI) for all infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 41.74 (39.21, 44.39), 48.73 (45.82, 51.77), 45.02 (43.10, 47.01), and 34.24 (32.07, 36.53) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.20 (1.10, 1.31), 1.36 (1.24, 1.49), and 1.28 (1.18, 1.38), respectively.

The IRs (95% CI) for serious infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 2.86 (2.41, 3.37), 3.64 (3.11, 4.23), 3.24 (2.89, 3.62), and 2.44 (2.02, 2.92) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.17 (0.92, 1.50), 1.48 (1.17, 1.87), and 1.32 (1.07, 1.63), respectively.

The IRs (95% CI) for opportunistic infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.76 (0.54, 1.04), 0.91 (0.66, 1.22), 0.84 (0.67, 1.04), and 0.42 (0.26, 0.64) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.82 (1.07, 3.09), 2.17 (1.29, 3.66), and 1.99 (1.23, 3.22), respectively. The majority of the opportunistic infections in the tofacitinib treatment arms were opportunistic herpes zoster infections; a limited number of events with tuberculosis were also reported. Excluding opportunistic herpes zoster infections and tuberculosis, the IRs (95% CI) for all

other opportunistic infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.08 (0.02, 0.20), 0.14 (0.06, 0.30), 0.11 (0.05, 0.20), and 0.06 (0.01, 0.17) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the hazard ratio (HR) (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.30 (0.29, 5.82), 2.40 (0.62, 9.29), and 1.84 (0.51, 6.59), respectively.

The IRs (95% CI) for herpes zoster (includes all herpes zoster events) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms) and TNF inhibitor were 3.75 (3.22, 4.34), 3.94 (3.38, 4.57), 3.84 (3.45, 4.26), and 1.18 (0.90, 1.52) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HR (95% CI) for herpes zoster with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 3.17 (2.36, 4.27), 3.33 (2.48, 4.48), and 3.25 (2.46, 4.29), respectively.

Serious Infections from Non-interventional Post Approval Safety Study

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

Thromboembolism

Venous Thromboembolism

The IRs (95% CI) for VTE for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms) and TNF inhibitor were 0.33 (0.19, 0.53), 0.70 (0.49, 0.99), 0.51 (0.38, 0.67), and 0.20 (0.10, 0.37) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HR (95% CI) for VTE with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.66 (0.76, 3.63), 3.52 (1.74, 7.12), and 2.56 (1.30, 5.05), respectively.

The IRs (95% CI) for PE for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms) and TNF inhibitor were 0.17 (0.08, 0.33), 0.50 (0.32, 0.74), 0.33 (0.23, 0.46), and 0.06 (0.01, 0.17) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HR (95% CI) for PE with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 2.93 (0.79, 10.83), 8.26 (2.49, 27.43), and 5.53 (1.70, 18.02), respectively. In tofacitinib-treated patients where PE was observed, the majority (97%) had VTE risk factors.

The IRs (95% CI) for DVT for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms) and TNF inhibitor were 0.21 (0.11, 0.38), 0.31 (0.17, 0.51), 0.26 (0.17, 0.38), and 0.14 (0.06, 0.29) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HR (95% CI) for DVT with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.54 (0.60, 3.97), 2.21 (0.90, 5.43), and 1.87 (0.81, 4.30), respectively.

In a post hoc exploratory biomarker analysis within a large randomized PASS in RA patients who were 50 years or older with at least one additional cardiovascular risk factor, occurrences of subsequent VTEs were observed more frequently in tofacitinib-treated patients with D-dimer level ≥2× ULN at 12 months treatment versus those with D-dimer level <2× ULN. This observation was not identified in TNFi-treated patients. Interpretation is limited by the low number of VTE events and restricted D-dimer test availability (only assessed at Baseline, Month 12, and at the end of the study). In patients who did not have a VTE during the study, mean D-dimer levels were significantly reduced at Month 12 relative to Baseline across all treatment arms. However, D-dimer levels ≥2× ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D-dimer testing in this study. Considering the data and the overall limitations of this post hoc exploratory biomarker analysis, there is limited utility of conducting D-dimer monitoring in the context of risk mitigation for VTE events.

Arterial Thromboembolism

The IRs (95% CI) for arterial thromboembolism (ATE) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms) and TNF inhibitor were 0.92 (0.68, 1.22), 0.94 (0.68, 1.25), 0.93 (0.75, 1.14), and 0.82 (0.59, 1.12) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HR (95% CI) for ATE with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.12 (0.74, 1.70), 1.14 (0.75, 1.74), and 1.13 (0.78, 1.63), respectively.

Major Adverse Cardiovascular Events (MACE), Including Myocardial Infarction

MACE includes non-fatal myocardial infarction, non-fatal stroke, and cardiovascular deaths excluding fatal pulmonary embolism. The IRs (95% CI) for MACE for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.91 (0.67, 1.21), 1.05 (0.78, 1.38), 0.98 (0.79, 1.19), and 0.73 (0.52, 1.01) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.24 (0.81, 1.91), 1.43 (0.94, 2.18), and 1.33 (0.91, 1.94), respectively.

In the tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib, and TNFi treatment arms, there were a total of 19, 19, 38, and 11 patients with MI events, respectively. Of these totals, the number of patients with fatal MI events was 0, 3, 3, and 3, respectively, whereas the number of patients with non-fatal MI events was 19, 16, 35, and 8, respectively. Therefore, the IRs that follow are for non-fatal MI. The IRs (95% CI) for non-fatal MI for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), 0.35 (0.24, 0.48), and 0.16 (0.07, 0.31) patients with events per 100 PYs,

respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 2.32 (1.02, 5.30), 2.08 (0.89, 4.86), and 2.20 (1.02, 4.75), respectively.

Malignancies Excluding NMSC

The IRs (95% CI) for malignancies excluding NMSC for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 1.13 (0.87, 1.45), 1.13 (0.86, 1.45), 1.13 (0.94, 1.35), and 0.77 (0.55, 1.04) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.47 (1.00, 2.18), 1.48 (1.00, 2.19), and 1.48 (1.04, 2.09), respectively.

The IRs (95% CI) for lymphoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), 0.09 (0.04, 0.17), and 0.02 (0.00, 0.10) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 3.99 (0.45, 35.70), 6.24 (0.75, 51.86), and 5.09 (0.65, 39.78), respectively.

The IRs (95% CI) for lung cancer for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.23 (0.12, 0.40), 0.32 (0.18, 0.51), 0.28 (0.19, 0.39), and 0.13 (0.05, 0.26) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.84 (0.74, 4.62), 2.50 (1.04, 6.02), and 2.17 (0.95, 4.93), respectively.

NMSC

The IRs (95% CI) for NMSC for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.61 (0.41, 0.86), 0.69 (0.47, 0.96), 0.64 (0.50, 0.82), and 0.32 (0.18, 0.52) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.90 (1.04, 3.47), 2.16 (1.19, 3.92), and 2.02 (1.17, 3.50), respectively.

The IRs (95% CI) for basal cell carcinoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.37 (0.22, 0.58), 0.33 (0.19, 0.54), 0.35 (0.24, 0.49), and 0.26 (0.14, 0.44) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 1.43 (0.71, 2.90), 1.28 (0.61, 2.66), and 1.36 (0.72, 2.56), respectively.

The IRs (95% CI) for cutaneous squamous cell carcinoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.29 (0.16, 0.48), 0.45 (0.29, 0.69), 0.37 (0.26, 0.51), and 0.16 (0.07, 0.31) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice

daily, and all tofacitinib were 1.82 (0.77, 4.30), 2.86 (1.27, 6.43), and 2.32 (1.08, 4.99), respectively.

Gastrointestinal Perforations

The IRs (95% CI) for gastrointestinal perforations for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, all tofacitinib (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 0.17 (0.08, 0.33), 0.10 (0.03, 0.24), 0.14 (0.08, 0.23), and 0.08 (0.02, 0.20) patients with events per 100 PYs, respectively. Compared with TNF inhibitor, the HRs (95% CI) for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and all tofacitinib were 2.20 (0.68, 7.15), 1.29 (0.35, 4.80), and 1.76 (0.58, 5.34), respectively.

Fractures

The IRs (95% CI) for fractures for XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, all XELJANZ (combines 5 mg twice daily and 10 mg twice daily treatment arms), and TNF inhibitor were 2.79 (2.34, 3.30), 2.87 (2.40, 3.40), 2.83 (2.50, 3.19) and 2.27 (1.87, 2.74) patients with events per 100 PYs respectively. Compared with TNFi, the HRs (95% CI) for XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, and all XELJANZ were 1.23 (0.96, 1.58) 1.26 (0.97, 1.62) and 1.24 (0.99, 1.55) respectively.

Laboratory Tests

Liver enzyme tests

The percentages of patients with at least one post-baseline ALT elevation >1x ULN, 3x ULN, and 5x ULN for the tofacitinib 5 mg twice daily treatment arm were 52.83, 6.01, and 1.68, respectively. The percentages for the tofacitinib 10 mg twice daily treatment arm were 54.46, 6.54, and 1.97, respectively. The percentages for all tofacitinib (combines tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily) were 53.64, 6.27, and 1.82, respectively. The percentages for the TNF inhibitor treatment arm were 43.33, 3.77, and 1.12, respectively.

The percentages of patients with at least one post-baseline AST elevation >1x ULN, 3x ULN, and 5x ULN for the tofacitinib 5 mg twice daily treatment arm were 45.84, 3.21, and 0.98, respectively. The percentages for the tofacitinib 10 mg twice daily treatment arm were 51.58, 4.57, and 1.62, respectively. The percentages for all tofacitinib (combines tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily) were 48.70, 3.89, and 1.30, respectively. The percentages for the TNF inhibitor treatment arm were 37.18, 2.38, and 0.70, respectively.

Lipids

At 12 months, in the tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor treatment arms, the mean percent increase in LDL cholesterol was 13.80, 17.04, and 5.50, respectively. At 24 months, the mean percent increase was 12.71, 18.14, and 3.64, respectively.

At 12 months, in the tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor treatment arms, the mean percent increase in HDL cholesterol was 11.71, 13.63, and 2.82, respectively. At 24 months, the mean percent increase was 11.58, 13.54, and 1.42, respectively.

Clinical Efficacy

Rheumatoid Arthritis

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

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

Study II was a 12-month study in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a non-biologic DMARD received tofacitinib 5 or 10 mg twice daily or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments, such as azathioprine or cyclosporine). At the Month 3 visit, non-responding patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 or 10 mg twice daily. At the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3 and rates of DAS28-4(ESR) <2.6 at Month 6.

Study III was a 12-month study in which 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX. Patients received tofacitinib 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6. Study III was not designed as a head-to-head comparison between tofacitinib and adalimumab.

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

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

Clinical Response

ACR Response

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

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.

During the 3 month (Studies I and V) and 6 month (Studies II, III, and IV) controlled portions of the studies, patients treated with tofacitinib at a dose of 10 mg twice daily generally had higher response rates compared to patients treated with tofacitinib 5 mg twice daily. In Study III, the primary endpoints were the proportion achieving an ACR20 response at Month 6; change in HAQ-DI at Month 3, and DAS28-4(ESR) <2.6 at Month 6. The data for these primary outcomes were 51.5, 52.6, 47.2 and 28.3%; -0.55, -0.61, -0.49 and -0.24; and 6.2%, 12.5%, 6.7% and 1.1% for the 5 mg twice daily tofacitinib, 10 mg twice daily tofacitinib, adalimumab 40 mg subcutaneously every other week and placebo groups, respectively. For a pre-specified secondary endpoint, the ACR70 response rates at Month 6 for the 5 mg twice daily and 10 mg twice daily tofacitinib groups were significantly greater than adalimumab 19.9%, 21.9% and 9.1%, respectively.

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, or disease status. Time to onset was rapid (as early as Week 2 in Studies I, II and V) and the magnitude of response continued to improve with duration of treatment. As with the overall ACR response in patients treated with 5 mg or 10 mg twice daily tofacitinib, each of the components of the ACR response was consistently improved from baseline including: tender and swollen joint counts; patient and physician global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs in all studies.

DAS28-4(ESR) Response

Patients in the Phase 3 studies had a mean Disease Activity Score (DAS28-4[ESR]) of 6.1-6.7 at baseline. Significant reductions in DAS28-4(ESR) from baseline (mean improvement) of 1.8-2.0 and 1.9-2.2 were observed in 5 mg and 10 mg tofacitinib-treated patients, respectively, compared to placebo-treated patients (0.7-1.1) at 3 months. The

proportion of patients achieving a DAS28 clinical remission (DAS28-4(ESR) <2.6) in Studies II, III and IV was significantly higher in patients receiving 5 mg or 10 mg tofacitinib (6-9% and 13-16%, respectively) compared to 1-3% of placebo patients at 6 months. In Study III, the percentages of patients achieving DAS28-4(ESR) <2.6 observed for tofacitinib 5 mg twice daily, 10 mg twice daily, and adalimumab at Month 6 were 6.2%, 12.5%, and 6.7%, respectively.

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

Table 6: Proportion of Patients with an ACR Response

Study I: DMARD Inadequate Responders				
Response Rate (%)	**Time**	**Placebo** **N=120**	**Tofacitinib 5 mg Twice Daily Monotherapy** **N=241**	**Tofacitinib 10 mg Twice Daily Monotherapy** **N=242**
ACR20	Month 3	27	60	66
	Month 6	NA	69	71
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
ACR50	Month 3	13	31	37
	Month 6	NA	42	47
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
ACR70	Month 3	6	15	20
	Month 6	NA	22	29
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
Study II: DMARD Inadequate Responders DMARD(s), Most Commonly MTX				
Response Rate (%)	**Time**	**Placebo** **N=157**	**Tofacitinib 5 mg Twice Daily DMARD(s)** **N=311**	**Tofacitinib 10 mg DMARD(s)** **N=309**
ACR20	Month 3	27	56	65
	Month 6	31	53	58
	Month 12	NA	51	57
ACR50	Month 3	10	27	34
	Month 6	13	34	37
	Month 12	NA	33	43
ACR70	Month 3	2	8	14
	Month 6	3	13	16
	Month 12	NA	19	26
Study IV: MTX Inadequate Responders				
Response Rate (%)	**Time**	**Placebo + MTX** **N=154**	**Tofacitinib 5 mg Twice Daily+ MTX** **N=309**	**Tofacitinib 10 mg Twice Daily+ MTX** **N=309**
ACR20	Month 3	27	56	66
	Month 6	25	51	62
	Month 12	NA	49	56

	Month 24	NA	41	50
ACR50	Month 3	8	29	36
	Month 6	8	32	44
	Month 12	NA	32	39
	Month 24	NA	29	40
ACR70	Month 3	3	11	17
	Month 6	1	15	22
	Month 12	NA	19	27
	Month 24	NA	17	26
Study V: TNF Inhibitor Inadequate Responders				
Response Rate (%)	**Time**	**Placebo + MTX** **N=131**	**Tofacitinib 5 mg Twice Daily+ MTX** **N=132**	**Tofacitinib 10 mg Twice Daily+ MTX** **N=133**
ACR20	Month 3	24	42	48
	Month 6	NA	52	55
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
ACR50	Month 3	8	27	28
	Month 6	NA	37	30
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA
ACR70	Month 3	2	14	11
	Month 6	NA	16	16
	Month 12	NA	NA	NA
	Month 24	NA	NA	NA

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

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

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

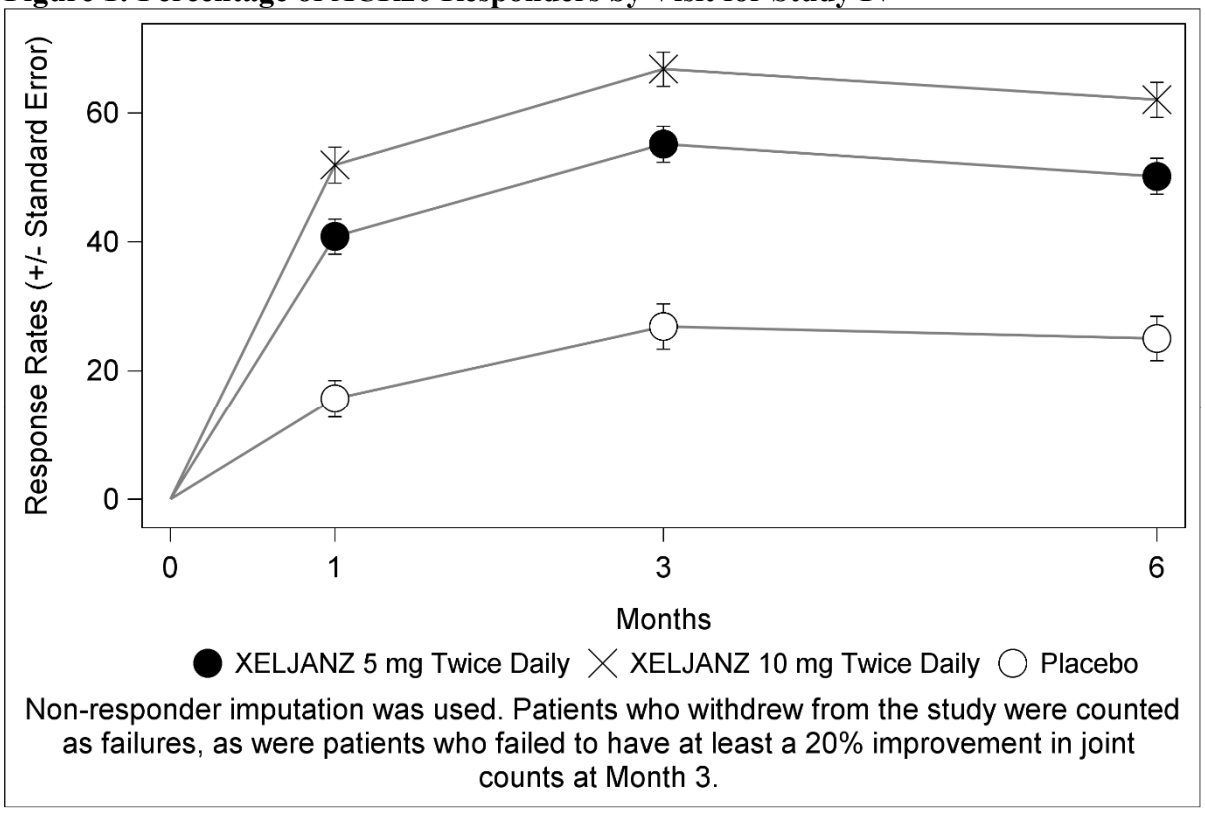
Study IV: MTX Inadequate Responders				
Component	**Time**	**Placebo + MTX** **N=156**	**Tofacitinib 5 mg Twice Daily + MTX** **N=316**	**Tofacitinib 10 mg Twice Daily + MTX** **N=309**
Number of tender joints (0-68)	Baseline	23	24	23
	Month 3	18	13	10
Number of swollen joints (0-66)	Baseline	14	14	14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

Study V: TNF Inhibitor Inadequate Responders				
Component	**Time**	**Placebo + MTX** **N=132**	**Tofacitinib 5 mg Twice Daily + MTX** **N=133**	**Tofacitinib 10 mg Twice Daily + MTX** **N=134**
Number of tender joints (0-68)	Baseline	28	28	28
	Month 3	21	16	13
Number of swollen joints (0-66)	Baseline	17	16	17
	Month 3	12	8	7
Pain[a]	Baseline	61	66	60
	Month 3	53	39	38
Patient global assessment[a]	Baseline	62	65	59
	Month 3	53	41	37
Disability index (HAQ-DI)[b]	Baseline	1.63	1.60	1.50
	Month 3	1.44	1.20	1.10
Physician global assessment[a]	Baseline	64	65	59
	Month 3	44	35	31
CRP (mg/L)	Baseline	16.7	19.3	15.7
	Month 3	18.2	6.2	4.8

[a] Visual analog scale: 0 = best, 100 = worst
[b] Health Assessment Questionnaire Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities

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

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



Physical Function Response and Health-related Outcomes

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving tofacitinib 5 and 10 mg twice daily demonstrated significantly greater improvement from baseline in physical functioning compared to placebo at Month 3 (Studies I, II, III, and V) and Month 6 (Studies II and III). Tofacitinib 5 or 10 mg twice daily-treated patients exhibited significantly greater improved physical functioning compared to placebo as early as Week 2 in Studies I and II. In Study III, mean HAQ-DI improvements were maintained to 12 months in tofacitinib-treated patients. Mean HAQ-DI improvements were maintained for 36 months in the ongoing open-label extension studies. Compared with adalimumab-treated patients, at Month 3, patients in the tofacitinib 5 mg twice daily had similar decreases from baseline in HAQ-DI values and patients in 10 mg twice daily group had significantly greater decreases in HAQ-DI. The mean change in HAQ-DI from baseline to Month 3 in Studies I to V are shown in Table 8.

Table 8: Mean Change from Baseline in HAQ-DI

Study I: DMARD Inadequate Responders				
Time	**Placebo** **N=109**	**Tofacitinib 5 mg Monotherapy Twice Daily** **N=237**	**Tofacitinib 10 mg Twice Daily Monotherapy** **N=227**	
LS Mean Change in HAQ-DI at Month 3[a]	-0.19	-0.50**	-0.57**	
Study II: DMARD Inadequate Responders				
	Placebo + DMARD(s) **N=147**	**Tofacitinib 5 mg Twice Daily + DMARD(s)** **N=292**	**Tofacitinib 10 mg Twice Daily + DMARD(s)** **N=292**	
LS Mean Change in HAQ-DI at Month 3[a]	-0.21	-0.46**	-0.56**	
Study III: MTX Inadequate Responders				
	Placebo + MTX **N=98**	**Tofacitinib 5 mg Twice Daily + MTX** **N=188**	**Tofacitinib 10 mg Twice Daily + MTX** **N=185**	**Adalimumab 40 mg QOW + MTX** **N=190**
LS Mean Change in HAQ-DI at Month 3[a]	-0.24	-0.55**	-0.61**	-0.49**
Study IV: MTX Inadequate Responders				
	Placebo + MTX **N=146**	**Tofacitinib 5 mg Twice Daily + MTX** **N=294**	**Tofacitinib 10 mg Twice Daily + MTX** **N=300**	
LS Mean Change in HAQ-DI at Month 3[a]	-0.15	-0.40[b]	-0.54	
Study V: TNF Inhibitor Inadequate Responders				
	Placebo **N=118**	**Tofacitinib 5 mg Twice Daily + MTX** **N=117**	**Tofacitinib 10 mg Twice Daily + MTX** **N=125**	
LS Mean Change in HAQ-DI at Month 3[a]	-0.18	-0.43**	-0.46**	

[a] Primary efficacy time point.
[b] Statistical significance could not be declared in Study IV due to step-down procedure.
** p<0.0001, tofacitinib vs. placebo + MTX/DMARD
Results are obtained from a longitudinal linear model with change from baseline as a dependent variable and treatment, baseline, visit, region as fixed effects and patient as random effect.
CI = confidence interval, FAS = full analysis set, LS = least squares, N = number of patients, MTX = methotrexate, QOW = every other week, HAQ-DI = Health Assessment Questionnaire – Disability Index

Other Health-related Outcomes

Health-related quality of life was assessed by the Short Form Health Survey (SF-36) in all 5 studies. In these studies, patients receiving tofacitinib 10 mg twice daily demonstrated significantly greater improvement from baseline compared to placebo in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 at Month 3. Both tofacitinib-treated groups exhibited significantly greater improvement from baseline compared to placebo in all 8 domains as well as PCS and MCS at Month 3 in Studies I, IV, and V. In Studies III and IV, mean SF-36 improvements were maintained to 12 months in tofacitinib-treated patients.

Improvement in fatigue was evaluated by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale at Month 3 in all studies. Patients receiving tofacitinib 5 or 10 mg twice daily demonstrated significantly greater improvement from baseline in fatigue compared to placebo in all 5 studies. In Studies III and IV, mean FACIT-F improvements were maintained to 12 months in tofacitinib-treated patients.

Improvement in sleep was assessed using the Sleep Problems Index I and II summary scales of the Medical Outcomes Study Sleep (MOS-Sleep) measure at Month 3 in all studies. Patients receiving tofacitinib 5 or 10 mg twice daily demonstrated significantly greater improvement from baseline in both scales compared to placebo in Studies II, III, and IV. In Studies III and IV, mean improvements in both scales were maintained to 12 months in tofacitinib-treated patients.

Improvement in productivity was evaluated using the Work Limitations Questionnaire (WLQ) scale at Month 3 in all studies. Patients receiving tofacitinib 10 mg twice daily demonstrated significantly greater improvement from baseline in the Overall Output Summary Scale compared to placebo in Studies III, IV, and V. In Studies III and IV, mean Overall Output improvements were maintained to 12 months in tofacitinib 10 mg twice daily-treated patients.

Durability of Clinical Responses

Durability of effect was assessed by ACR20, ACR50, ACR70 response rates, mean HAQ-DI, and mean DAS28-4(ESR) in the three Phase 3 DMARD IR studies with duration of at least one year. Efficacy was maintained in all tofacitinib treatment groups through to the end of the studies. Evidence of persistence of efficacy with tofacitinib treatment for up to 6 years is also provided from data in a large randomized PASS in RA patients 50 years and older with at least one additional CV risk factor, as well as in completed open-label, long-term follow-up studies up to 8 years.

Psoriatic Arthritis

The efficacy and safety of tofacitinib were assessed in 2 randomized, double-blind, placebo-controlled Phase 3 studies in adult patients with active PsA (≥3 swollen and ≥3 tender joints). Patients were required to have active plaque psoriasis at the screening visit. 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, 9.5% of patients received concomitant sulfasalazine, and 5.7% of patients received concomitant leflunomide. The median PsA disease duration was 3.8 years. At baseline, 79.9% and 56.2% of patients had enthesitis and dactylitis, respectively. Patients randomized to tofacitinib received 5 mg twice daily or tofacitinib 10 mg twice daily for 12 months. Patients randomized to placebo were advanced in a blinded manner at Month 3 to either tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily and received treatment until Month 12. Patients randomized 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, 15.7% of patients received concomitant sulfasalazine, and 8.6% of patients received concomitant leflunomide. The median PsA disease duration was 7.5 years. At baseline, 80.7% and 49.2% of patients had enthesitis and dactylitis, respectively. Patients randomized to tofacitinib received 5 mg twice daily or tofacitinib 10 mg twice daily for 6 months. Patients randomized to placebo were advanced in a blinded manner at Month 3 to either tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily and received treatment until Month 6.

Signs and Symptoms

Treatment with tofacitinib resulted in significant improvements in some signs and symptoms of PsA, as assessed by the ACR20 response criteria compared to placebo at Month 3. The efficacy results for 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

	Conventional synthetic DMARD inadequate responders[a] (TNFi-Naïve)			**TNFi inadequate responders[b]**	
	OPAL BROADEN			**OPAL BEYOND[c]**	
Treatment group	**Placebo**	**Tofacitinib 5 mg twice daily**	**Adalimumab 40 mg SC q2W**	**Placebo**	**Tofacitinib 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 randomized and treated patients; NA=Not applicable, as data for placebo treatment is not available beyond month 3 due to placebo advanced to tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily; SC q2w=subcutaneously once every 2 weeks; TNFi=tumor 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 tofacitinib 5 mg BID-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 tofacitinib. The number of patients with arthritis mutilans or axial involvement was too small to allow meaningful assessment. Statistically significant ACR20 response rates were observed with tofacitinib 5 mg BID in both studies as early as Week 2 (first post-baseline assessment) in comparison to placebo.

In OPAL BROADEN, Minimal Disease Activity (MDA) response was achieved by 26.2%, 25.5% and 6.7% of tofacitinib 5 mg BID, adalimumab and placebo treated patients, respectively (tofacitinib 5 mg BID treatment difference from placebo 19.5% [95% CI: 9.9, 29.1]) at Month 3. In OPAL BEYOND, MDA was achieved by 22.9% and 14.5% of tofacitinib 5 mg BID and placebo treated patients, respectively, however tofacitinib 5 mg BID did not achieve nominal statistical significance (treatment difference from placebo 8.4% [95% CI: -1.0, 17.8] at Month 3).

Radiographic Response

In study OPAL BROADEN, the progression of structural joint damage was assessed radiographically utilizing 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 tofacitinib 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 tofacitinib 5 mg twice daily demonstrated greater improvement ($p \leq 0.05$) from baseline in physical functioning compared to placebo at Month 3 (see Table 10).

Table 10: Change from Baseline in HAQ-DI in PsA Studies OPAL BROADEN and OPAL BEYOND

	Least squares mean change from baseline in HAQ-DI				
	Conventional synthetic DMARD inadequate responders[a] (TNFi-naïve)			**TNFi inadequate responders[b]**	
	OPAL BROADEN			**OPAL BEYOND**	
Treatment group	**Placebo**	**Tofacitinib 5 mg twice daily**	**Adalimumab 40 mg SC q2W**	**Placebo**	**Tofacitinib 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 $p \leq 0.05$; [***] 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=tumor 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 at least one TNF inhibitor (TNFi) due to lack of efficacy and/or intolerability.
[c] Achieved statistical significance globally at $p \leq 0.05$ 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 tofacitinib 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, fatigue was assessed by the FACIT-F. Patients receiving tofacitinib 5 mg twice daily demonstrated greater improvement from baseline compared to placebo in the SF-36v2 physical functioning domain, the SF-36v2 physical component summary score, and FACIT-F scores at month 3 in studies OPAL BROADEN and OPAL BEYOND (nominal $p \leq 0.05$). Improvements from baseline in SF-36v2 and FACIT-F were maintained through Month 6 (OPAL BROADEN and OPAL BEYOND) and Month 12 (OPAL BROADEN).

Patients receiving tofacitinib 5 mg twice daily demonstrated a greater improvement in arthritis pain (as measured on a 0-100 visual analogue scale) from baseline at Week 2 (first post-baseline assessment) through Month 3 compared to placebo in studies OPAL BROADEN and OPAL BEYOND (nominal $p \leq 0.05$).

Ulcerative Colitis

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

Table 11 provides additional information regarding pertinent study design and population characteristics.

Table 11: Phase 3 Clinical Studies of Tofacitinib 5 mg and 10 mg Twice Daily Doses in Patients with UC

	OCTAVE Induction 1	**OCTAVE Induction 2**	**OCTAVE Sustain**
Treatment groups (randomization ratio)	**Tofacitinib 10 mg twice daily placebo (4:1)**	**Tofacitinib 10 mg twice daily placebo (4:1)**	**Tofacitinib 5 mg twice daily Tofacitinib 10 mg twice daily placebo (1:1:1)**
Number of patients enrolled	598	541	593
Study duration	8 weeks	8 weeks	52 weeks
Primary efficacy endpoint	Remission	Remission	Remission
Key secondary efficacy endpoints	Improvement of endoscopic appearance of the mucosa	Improvement of endoscopic appearance of the mucosa	Improvement of endoscopic appearance of the mucosa Sustained corticosteroid-free remission among patients in remission at baseline
Prior TNFi failure	51.3%	52.1%	44.7%
Prior corticosteroid failure	74.9%	71.3%	75.0%
Prior immunosuppressant failure	74.1%	69.5%	69.6%
Baseline corticosteroid use	45.5%	46.8%	50.3%

Abbreviations: TNFi=tumor necrosis factor inhibitor; UC=ulcerative colitis.

In addition, safety and efficacy of tofacitinib were assessed in an open-label long-term extension study (OCTAVE Open). Patients who completed 1 of the induction studies (OCTAVE Induction 1 or OCTAVE Induction 2) but did not achieve clinical response or patients who completed or withdrew early due to treatment failure in the maintenance study (OCTAVE Sustain) were eligible for OCTAVE Open. Patients from OCTAVE Induction 1 or OCTAVE Induction 2 who did not achieve clinical response after 8 weeks in OCTAVE Open

were to be discontinued from OCTAVE Open. Corticosteroid tapering was also required upon entrance into OCTAVE Open.

Induction Efficacy Data (OCTAVE Induction 1 and OCTAVE Induction 2)

The primary endpoint of OCTAVE Induction 1 and OCTAVE Induction 2 was the proportion of patients in remission at Week 8, 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.

A significantly greater proportion of patients treated with tofacitinib 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**	
Endpoint	**Placebo**	**Tofacitinib 10 mg twice daily**	**Placebo**	**Tofacitinib 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%*
Normalization 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**	**Tofacitinib 10 mg twice daily**	**Placebo**	**Tofacitinib 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%*
Normalization 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] Normalization 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 tofacitinib 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		
Endpoint	**Placebo N=122**	**Tofacitinib 10 mg twice daily N=476**
Remission[a]		
With prior TNF inhibitor failure	1.6% (1/64)	11.1% (27/243)
Without prior TNF inhibitor failure[b]	15.5% (9/58)	26.2% (61/233)
Improvement of endoscopic appearance of the mucosa[c]		
With prior TNF inhibitor failure	6.3% (4/64)	22.6% (55/243)
Without prior TNF inhibitor failure[b]	25.9% (15/58)	40.3% (94/233)
OCTAVE induction study 2		
Endpoint	**Placebo N=112**	**Tofacitinib 10 mg twice daily N=429**
Remission[a]		
With prior TNF inhibitor failure	0.0% (0/60)	11.7% (26/222)
Without prior TNF inhibitor failure[b]	7.7% (4/52)	21.7% (45/207)
Improvement of endoscopic appearance of the mucosa[c]		
With prior TNF inhibitor failure	6.7% (4/60)	21.6% (48/222)
Without prior TNF inhibitor failure[b]	17.3% (9/52)	35.7% (74/207)

TNF=tumor 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).

As early as Week 2, the earliest scheduled study visit, and at each visit thereafter, significant differences were observed between tofacitinib 10 mg twice daily and placebo in the change from baseline in rectal bleeding and stool frequency, and partial Mayo score.

Maintenance (OCTAVE Sustain)

Patients who completed 8 weeks in 1 of the induction studies and achieved clinical response were re randomized into OCTAVE Sustain; 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 tofacitinib 5 mg twice daily and tofacitinib 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, as shown in Table 14.

Table 14: Proportion of Patients Meeting Efficacy Endpoints at Week 52 (OCTAVE Sustain)

	Central endoscopy read			**Local endoscopy read**		
Endpoint	**Placebo N=198**	**Tofacitinib 5 mg twice daily N=198**	**Tofacitinib 10 mg twice daily N=197**	**Placebo N=198**	**Tofacitinib 5 mg twice daily N=198**	**Tofacitinib 10 mg twice daily N=197**
Remission[a]	11.1%	34.3%*	40.6%*	13.1%	39.4%*	47.7%*
Improvement of endoscopic appearance of the mucosa[b]	13.1%	37.4%*	45.7%*	15.7%	44.9%*	53.8%*
Normalization of endoscopic appearance of the mucosa[c]	4.0%	14.6%**	16.8%*	5.6%	22.2%*	29.4%*
Maintenance of clinical response[d]	20.2%	51.5%*	61.9%*	20.7%	51.0%*	61.4%*
Remission among patients in remission at baseline[a,f]	10.2%	46.2%*	56.4%*	11.9%	50.8%*	65.5%*
Sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline[e,f]	5.1%	35.4%*	47.3%*	11.9%	47.7%*	58.2%*
Corticosteroid-free remission among patients taking corticosteroids at baseline[a,g]	10.9%	27.7%†	27.6%†	13.9%	32.7%†	31.0%†

* p<0.0001; **p<0.001; †p<0.05 for tofacitinib versus placebo.
N=number of patients in the analysis set.
[a] Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.
[b] Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).
[c] Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0.
[d] Maintenance of clinical response was defined by a decrease from the induction study (OCTAVE Induction 1, OCTAVE Induction 2) baseline Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the rectal bleeding subscore of ≥1 point or rectal bleeding subscore of 0 or 1. Patients were to be in clinical response at baseline of the maintenance study OCTAVE Sustain.
[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.
[f] N=59 for placebo, N=65 for tofacitinib 5 mg twice daily, N=55 for tofacitinib 10 mg twice daily.
[g] N=101 for placebo, N=101 for tofacitinib 5 mg twice daily, N=87 for tofacitinib 10 mg twice daily.

In both subgroups of patients with or without prior TNF inhibitor failure, a greater proportion of patients treated with either tofacitinib 5 mg twice daily or tofacitinib 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 15). This treatment difference from placebo was similar between tofacitinib 5 mg twice daily and tofacitinib 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 tofacitinib 10 mg twice daily than tofacitinib 5 mg twice daily by 9.7 to 16.7 percentage points across the primary and key secondary endpoints.

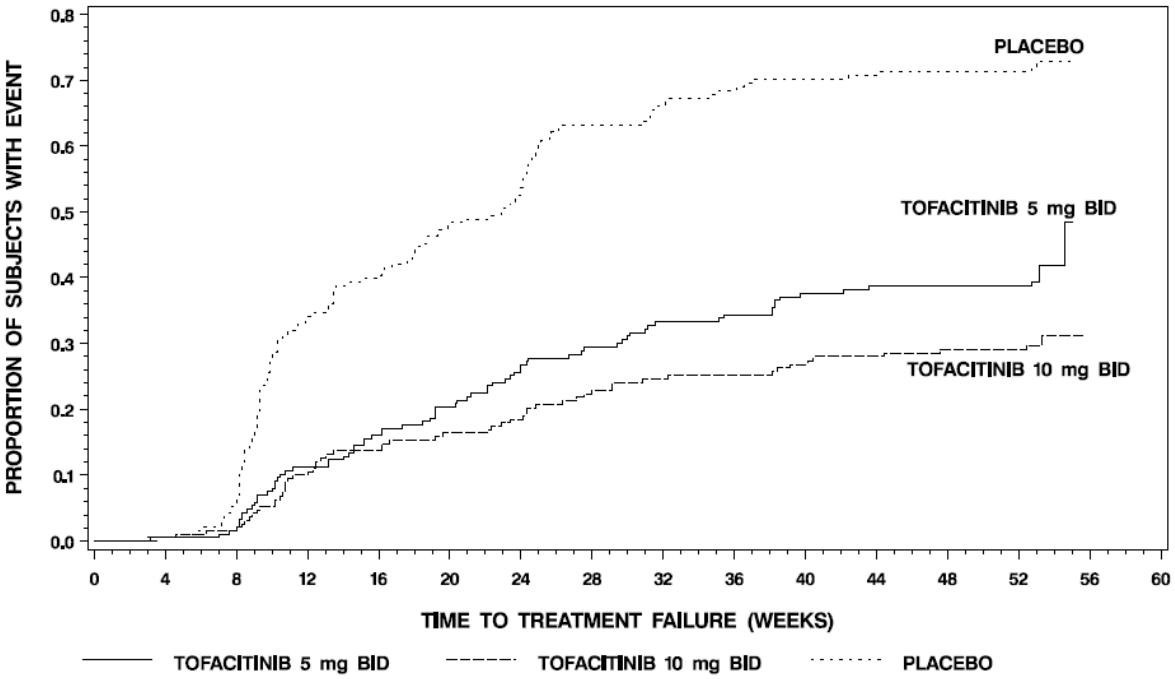
Table 15: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 52 by TNF Inhibitor Therapy Subgroup (OCTAVE Sustain, Central Endoscopy Read)

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

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

The proportion of patients in both tofacitinib 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, as shown in Figure 2.

Figure 2. Time to Treatment Failure in Maintenance Study OCTAVE Sustain (Kaplan-Meier Curves)



p<0.0001 for tofacitinib 5 mg twice daily versus placebo.
p<0.0001 for tofacitinib 10 mg twice daily versus placebo.
BID=twice daily.
Treatment failure was defined as an increase in Mayo score of ≥3 points from maintenance study baseline, accompanied by an increase in rectal bleeding subscore by ≥1 point, and an increase of endoscopic subscore of ≥1 point yielding an absolute endoscopic subscore of ≥2 after a minimum treatment of 8 weeks in the study.

Health-related and Quality of Life Outcomes

Tofacitinib 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). In the maintenance study (OCTAVE Sustain), tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily demonstrated greater maintenance of improvement compared to placebo in PCS and MCS scores, and in all 8 domains of the SF-36 at Week 24 and Week 52.

Tofacitinib 10 mg twice daily demonstrated greater improvement from baseline compared to placebo at week 8 in the total and all 4 domain scores of the Inflammatory Bowel Disease Questionnaire (IBDQ) (bowel symptoms, systemic function, emotional function, and social function) in the induction studies (OCTAVE Induction 1, OCTAVE Induction 2). In the maintenance study (OCTAVE Sustain), tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily demonstrated greater maintenance of improvement compared to placebo in the total and all 4 domain scores of the IBDQ at Week 24 and Week 52.

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 both induction and maintenance studies compared to placebo.

Open-label Extension Study (OCTAVE Open)

Patients who did not achieve clinical response in one of the induction studies (OCTAVE Induction 1 or OCTAVE Induction 2) after 8 weeks of tofacitinib 10 mg twice daily were allowed to enter an open-label extension study (OCTAVE Open). After an additional 8 weeks of tofacitinib 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 1 of the induction studies (OCTAVE Induction 1 or OCTAVE Induction 2) with tofacitinib 10 mg twice daily but experienced treatment failure after their dose was reduced to tofacitinib 5 mg twice daily or following treatment interruption in OCTAVE Sustain (i.e., were randomized to placebo), had their dose increased to tofacitinib 10 mg twice daily in OCTAVE Open. After 8 weeks on tofacitinib 10 mg twice daily in OCTAVE Open, remission was achieved in 35% (20/58) patients who received tofacitinib 5 mg twice daily in OCTAVE Sustain and 40% (40/99) patients with dose interruption in OCTAVE Sustain. 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 tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily remained in remission while receiving tofacitinib 5 mg twice daily.

5.2. Pharmacokinetic properties

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

Absorption and Distribution

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

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

Metabolism and Elimination

Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged drug, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of tofacitinib is attributed to the parent molecule. *In vitro*, tofacitinib is a substrate for multidrug resistance (MDR) 1, but not for breast cancer

resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1/1B3, or organic cationic transporter (OCT) 1/2, and is not an inhibitor of MDR1, OAT P1B1/1B3, OCT2, organic anion transporter (OAT) 1/3, or multidrug resistance associated protein (MRP) at clinically meaningful concentrations.

Pharmacokinetic data and dosing recommendations for special populations and drug interactions are provided in Figure 3.

Modifications required for special populations are described in Section 4.2 Posology and method of administration.

Pharmacokinetics in RA Patients

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

Pharmacokinetics in Patients with Active Psoriatic Arthritis / Moderate to Severe UC

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

Renal Impairment

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

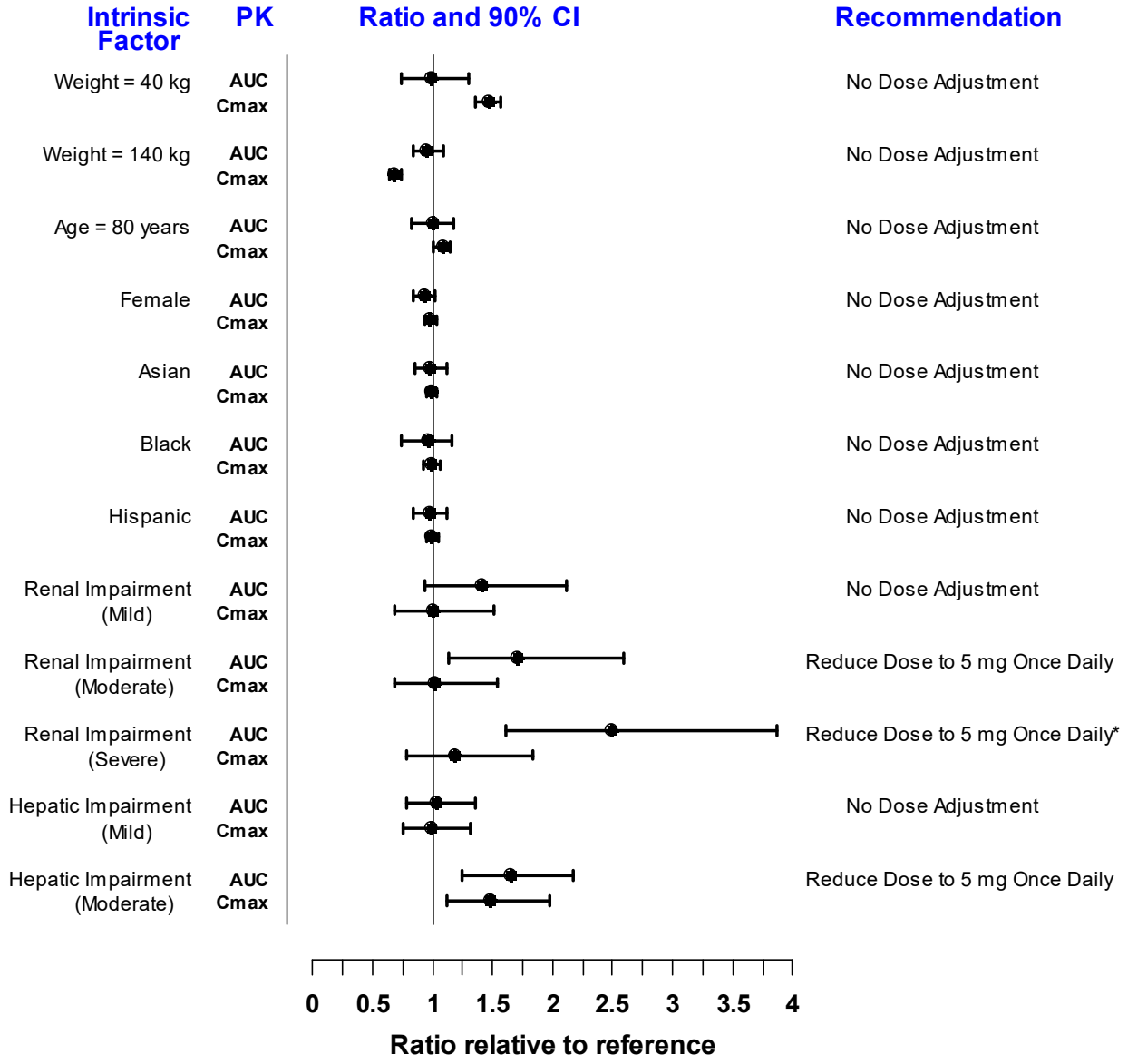
Hepatic Impairment

Patients with mild and moderate hepatic impairment had 3%, and 65% higher AUC, respectively, compared with healthy patients. Patients with severe hepatic impairment were not studied (see Section 4.2 Posology and method of administration).

Pediatric Population

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

Figure 3: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics



*Supplemental doses are not necessary in patients after dialysis.

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.

5.3. Non-clinical safety data

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

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

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Film Coat for 5 mg tablets: Opadry® II White (*33G28523*) *containing*:
HPMC 2910/Hypromellose 6cP
Titanium dioxide
Lactose monohydrate
Macrogol/PEG3350
Triacetin (glycerol triacetate)

6.2. Incompatibilities

Not applicable

6.3. Shelf-life

Refer to the outer carton.

6.4. Special precautions for storage

Store below 30°C. Store in the original package as the tablet may be sensitive to moisture.

6.5. Nature and contents of container

Foil/foil blisters containing 14 film-coated tablets.
Foil/foil blisters containing 56 film-coated tablets.
(*Not all pack sizes may be marketed*)

6.6. Special precautions for disposal and other handling

No special requirements.

7. PRODUCT OWNER

Pfizer Inc.
New York,
United States

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