Tofacitinib Tablets (XELJANZ®)

1. GENERIC NAME

Tofacitinib citrate Tablets 5 mg (XELJANZ®)

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.

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 (E464), Titanium Dioxide (E171), Lactose Monohydrate, Macrogol/PEG3350, Triacetin (Glycerol Triacetate).

3. DOSAGE FORM AND STRENGTH

Dosage Form: White, round, immediate-release film-coated tablets for oral use, debossed with "Pfizer" on one side, and "JKI 5" on the other side.

Strength: 5 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Rheumatoid Arthritis

Tofacitinib is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

Limitations of Use: Use of Tofacitinib in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Psoriatic Arthritis
Tofacitinib is indicated for the treatment of adult patients with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to methotrexate or other non-biologic disease-modifying antirheumatic drugs (DMARDs).

- Limitations of Use: Use of Tofacitinib in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ankylosing Spondylitis
Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

Limitations of Use: Use of Tofacitinib in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ulcerative Colitis
Tofacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have an inadequate response and who are intolerant to TNF blockers.

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

4.2 Posology and method of administration

Important Administration Instructions

- Do not initiate Tofacitinib in patients with an absolute lymphocyte count less than 500 cells/mm^3, an absolute neutrophil count (ANC) less than 1000 cells/mm^3 or who have hemoglobin levels less than 9 g/dL.
- Dose interruption is recommended for management of lymphopenia, neutropenia and anemia (see sections 4.4 and 4.8).
- Interrupt use of tofacitinib if a patient develops a serious infection until the infection is controlled (see section 4.4).
- Take Tofacitinib with or without food (see section 5.3).

Recommended Dosage in Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

Table 1 displays the recommended adult daily dosage of Tofacitinib and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, in patients with moderate or severe renal impairment (including but not limited to those with severe insufficiency who are undergoing hemodialysis) or moderate hepatic impairment, with lymphopenia, neutropenia, or anemia.

Table 1: Recommended Dosage of Tofacitinib in Patients with Rheumatoid Arthritis, Psoriatic Arthritis[1], and Ankylosing Spondylitis

	Tofacitinib
Adult patients	5 mg twice daily
Patients receiving: • Strong CYP3A4 inhibitors (e.g., ketoconazole), or • a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole) (see section 4.5)	5 mg once daily
Patients with: • moderate or severe renal impairment (see section 4.6) • moderate hepatic impairment (see section 4.6*)	5 mg once daily
	For patients undergoing hemodialysis, dose should be administered after the dialysis session on dialysis days. If a dose was taken before the dialysis procedure, supplemental doses are not recommended in patients after dialysis.
Patients with lymphocyte count less than 500 cells/mm^3, confirmed by repeat testing	Discontinue dosing.
Patients with ANC 500 to 1000 cells/mm^3	Interrupt dosing. When ANC is greater than 1000, resume 5 mg twice daily.
Patients with ANC less than 500 cells/mm^3	Discontinue dosing.
Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL	Interrupt dosing until hemoglobin values have normalized.

[1] Tofacitinib is used in combination with nonbiologic disease modifying antirheumatic drugs (DMARDs) in psoriatic arthritis. The efficacy of Tofacitinib as a monotherapy has not been studied in psoriatic arthritis

* Use of Tofacitinib in patients with severe hepatic impairment is not recommended.

Method of Administration:

Tofacitinib is given orally with or without food.

Recommended Dosage in Ulcerative Colitis

Table 2 displays the recommended adult daily dosage of Tofacitinib and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, with moderate or severe renal impairment (including but not limited to those with severe insufficiency who are undergoing hemodialysis) or moderate hepatic impairment, with lymphopenia, neutropenia or anemia.

Table 2: Recommended Dosage of Tofacitinib in Patients with UC

	Tofacitinib tablet
Adult patients	**Induction:** 10 mg twice daily for at least 8 weeks (see section 5.2); evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed continue 10 mg twice daily for a maximum of 16 weeks. Discontinue 10 mg twice daily after 16 weeks if adequate therapeutic response is not achieved. **Maintenance:** 5 mg twice daily. For patients with loss of response during maintenance treatment, a dosage of 10 mg twice daily may be considered and limited to the shortest duration, with careful consideration of the benefits and risks for the individual patient. Use the lowest effective dose needed to maintain response.
Patients receiving: • Strong CYP3A4 inhibitors (e.g., ketoconazole), or • a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole) (see section 4.5)	If taking 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, reduce to 5 mg once daily.
Patients with: • moderate or severe renal impairment (see section 4.6) • moderate hepatic impairment (see section 4.6) *	If taking 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, reduce to 5 mg once daily.
	For patients undergoing hemodialysis, dose should be administered after the dialysis session on dialysis days. If a dose was taken before the dialysis procedure, supplemental doses are not recommended in patients after dialysis.
Patients with lymphocyte count less than 500 cells/mm^3, confirmed by repeat testing	Discontinue dosing.
Patients with ANC 500 to 1000 cells/mm^3	If taking 10 mg twice daily, reduce to 5 mg twice daily. When ANC is greater than 1000, increase to 10 mg twice daily based on clinical response. If taking 5 mg twice daily, interrupt dosing. When ANC is greater than 1000, resume 5 mg twice daily.
Patients with ANC less than 500 cells/mm^3	Discontinue dosing.
Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL	Interrupt dosing until hemoglobin values have normalized.

*Use of Tofacitinib in patients with severe hepatic impairment is not recommended.

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 tofacitinib. The most common serious infections reported with tofacitinib included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infection, 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.

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

Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

Avoid use of tofacitinib in patients with an active, serious infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tofacitinib. Tofacitinib 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 tofacitinib 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.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infections.

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 recommended (see section 4.2).

Tuberculosis

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

Anti-tuberculosis therapy should also be considered prior to administration of tofacitinib 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 physician with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating anti-tuberculosis 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.

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

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with tofacitinib. Post-marketing cases of hepatitis B reactivation have been reported in patients treated with Tofacitinib. The impact of tofacitinib on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with tofacitinib. The risk of herpes zoster is increased in patients treated with tofacitinib and appears to be higher in patients treated with tofacitinib in Japan and Korea.

Mortality

Rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular risk factor treated with Tofacitinib 5 mg twice a day or Tofacitinib 10 mg twice a day had a higher observed rate of all-cause mortality, including sudden cardiovascular death, compared to those treated with TNF blockers in a large, randomized, postmarketing safety study (RA Safety Study 1). The incidence rate of all-cause mortality per 100 patient-years was 0.88 for Tofacitinib 5 mg twice a day, 1.23 for Tofacitinib 10 mg twice a day, and 0.69 for TNF blockers (see section 5.2, Clinical Studies). Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Tofacitinib.

A dosage of Tofacitinib 10 mg twice daily is not recommended for the treatment of RA, PsA, or AS (see section 4.2).

For the treatment of UC, use Tofacitinib at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response (see section 4.2).

Malignancy and Lymphoproliferative Disorder

Malignancies, including lymphomas and solid cancers, were observed in clinical studies of tofacitinib (see section 4.8).

In RA Safety Study 1, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed in patients treated with Tofacitinib 5 mg twice a day or Tofacitinib 10 mg twice a day as compared with TNF blockers. The incidence rate of malignancies (excluding NMSC) per 100 patient-years was 1.13 for Tofacitinib 5 mg twice a day, 1.13 for Tofacitinib 10 mg twice a day, and 0.77 for TNF blockers. Patients who are current or past smokers are at additional increased risk (see section 5.2, Clinical Studies).

Lymphomas and lung cancers, which are a subset of all malignancies in RA Safety Study 1, were observed at a higher rate in patients treated with Tofacitinib 5 mg twice a day and Tofacitinib 10 mg twice a day compared to those treated with TNF blockers. The incidence rate of lymphomas per 100 patient-years was 0.07 for Tofacitinib 5 mg twice a day, 0.11 for Tofacitinib 10 mg twice a day, and 0.02 for TNF blockers. The incidence rate of lung cancers per 100 patient-years among current and past smokers was 0.48 for Tofacitinib 5 mg twice a day, 0.59 for Tofacitinib 10 mg twice a day, and 0.27 for TNF blockers (see section 5.2, Clinical Studies).

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Tofacitinib, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy while on treatment, and patients who are current or past smokers. A Tofacitinib 10 mg twice daily dosage is not recommended for the treatment of RA or PsA (see section 4.2).

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.

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

Non-melanoma Skin Cancer

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with tofacitinib. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

In the UC population, treatment with tofacitinib 10 mg twice daily was associated with greater risk of NMSC.

Major Adverse Cardiovascular Events

In RA Safety Study 1, RA patients who were 50 years of age and older with at least one cardiovascular risk factor treated with Tofacitinib 5 mg twice daily or Tofacitinib 10 mg twice daily had a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular

death, non-fatal myocardial infarction (MI), and non-fatal stroke, compared to those treated with TNF blockers. The incidence rate of MACE per 100 patient-years was 0.91 for Tofacitinib 5 mg twice a day, 1.11 for Tofacitinib 10 mg twice a day, and 0.79 for TNF blockers. The incidence rate of fatal or non-fatal myocardial infarction per 100 patient-years was 0.36 for Tofacitinib 5 mg twice a day, 0.39 for Tofacitinib 10 mg twice a day, and 0.20 for TNF blockers (see section 5.2, Clinical Studies). Patients who are current or past smokers are at additional increased risk.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Tofacitinib, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue Tofacitinib in patients that have experienced a myocardial infarction or stroke. A Tofacitinib 10 mg twice daily dosage is not recommended for the treatment of RA or PsA (see section 4.2).

Thrombosis
Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis, have occurred in patients treated with Tofacitinib and other Janus kinase (JAK) inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death (see section 4.4).

Patients with rheumatoid arthritis 50 years of age and older with at least one cardiovascular risk factor treated with Tofacitinib at both 5 mg or 10 mg twice daily compared to TNF blockers in RA Safety Study 1 had an observed increase in incidence of these events. The incidence rate of DVT per 100 patient-years was 0.22 for Tofacitinib 5 mg twice a day, 0.28 for Tofacitinib 10 mg twice a day, and 0.16 for TNF blockers. The incidence rate of PE per 100 patient-years was 0.18 for Tofacitinib 5 mg twice a day, 0.49 for Tofacitinib 10 mg twice a day, and 0.05 for TNF blockers (see section 5.2, Clinical Studies).

A dosage of tofacitinib 10 mg twice daily is not recommended for the treatment of RA, PsA, or AS (see section 4.2).

In a long-term extension study in patients with UC, five cases of pulmonary embolism were reported in patients taking tofacitinib 10 mg twice daily, including one death in a patient with advanced cancer.

Promptly evaluate patients with symptoms of thrombosis and discontinue tofacitinib in patients with symptoms of thrombosis.

Avoid tofacitinib in patients that may be at increased risk of thrombosis. For the treatment of UC, use tofacitinib at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response (see section 4.2).

Gastrointestinal Perforations
Events of gastrointestinal perforation have been reported in clinical studies with tofacitinib, although the role of JAK inhibition in these events is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs).

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

Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation (see section 4.8).

Hypersensitivity
Reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients receiving Tofacitinib. Some events were serious. If a serious hypersensitivity reaction occurs, promptly discontinue tofacitinib while evaluating the potential cause or causes of the reaction (see section 4.8).

Laboratory Abnormalities

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

Avoid initiation of tofacitinib treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3). In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3 treatment with tofacitinib is not recommended.

Monitor lymphocyte counts at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts (see section 4.2).

Neutropenia:
Treatment with tofacitinib was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo.

Avoid initiation of tofacitinib treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3). For patients who develop a persistent ANC of 500 to 1000 cells/mm^3, interrupt dosing until ANC is greater than equal to 1000 cells/mm^3. In patients who develop an ANC less than 500 cells/mm^3, treatment with tofacitinib is not recommended.

Monitor neutrophil counts at baseline and after 4 - 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on ANC results (see section 4.2).

Anemia:
Avoid initiation of tofacitinib treatment in patients with a low hemoglobin level (i.e., less than 9 g/dL). Treatment with tofacitinib should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment.

Monitor hemoglobin at baseline and after 4 - 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on hemoglobin results (see sections 4.2).

Liver Enzyme Elevations:
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 tofacitinib should be interrupted until this diagnosis has been excluded.

Lipid Elevations:
Treatment with tofacitinib was associated with dose-dependent increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. There were no clinically relevant changes in LDL/HDL cholesterol ratios. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed approximately 4 - 8 weeks following initiation of tofacitinib therapy.

Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

Vaccinations
Avoid use of live vaccines concurrently with tofacitinib. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

A patient experienced dissemination of the vaccine strain of *varicella zoster* virus, 16 days after vaccination with live attenuated (Zostavax) virus vaccine and 2 days after treatment start with tofacitinib 5 mg twice daily. 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 patient recovered after treatment with standard doses of antiviral medication.

Update immunizations in agreement with current immunization guidelines prior to initiating tofacitinib therapy.

4.5 Drug interactions

Table 3 includes drugs with clinically important drug interactions when administered concomitantly with Tofacitinib and instructions for preventing or managing them.

Table 3: Clinically Relevant Interactions Affecting Tofacitinib When Co-administered with Other Drugs

Strong CP3A4 Inhibitors (e.g., ketoconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of Tofacitinib is recommended (see sections 4.2 and 5.3)
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of Tofacitinib is recommended (see sections 4.2 and 5.3)
Strong CYP3A4 Inducers (e.g., rifampin)	
Clinical Impact	Decreased exposure to tofacitinib and may result in loss of or reduced clinical response
Intervention	Co-administration with Tofacitinib is not recommended (see section 5.3)
Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)	
Clinical Impact	Risk of added immunosuppression; coadministration with biologic DMARDs or potent immunosuppressants has not been studied in patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or ulcerative colitis.
Intervention	Coadministration with Tofacitinib is not recommended (see sections 4.1 and 5.3)

4.6 Use in special populations

All information provided in this section is applicable to tofacitinib as they contain the same active ingredient (tofacitinib).

Pregnancy

Risk Summary

Available data with Tofacitinib use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis in pregnancy (see Clinical Considerations). In animal reproduction studies, fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73-times and 6.3-times the maximum recommended dose of 10 mg twice daily, respectively. Further, in a peri and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73-times the recommended dose of 5 mg twice daily and approximately 36 times the maximum recommended dose of 10 mg twice daily, respectively (see Data).

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriages are 2 to 4% and 15 to 20% of clinically recognized pregnancies, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk
Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data
In a rat embryofetal developmental study, in which pregnant rats received tofacitinib during organogenesis, tofacitinib was teratogenic at exposure levels approximately 146 times the recommended dose of 5 mg twice daily, and approximately 73 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 100 mg/kg/day in rats). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively, and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). In addition, there was an increase in post-implantation loss, consisting of early and late resorptions, resulting in a reduced number of viable fetuses. Mean fetal body weight was reduced. No developmental toxicity was observed in rats at exposure levels approximately 58 times the recommended dose of 5 mg twice daily, and approximately 29 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in pregnant rats).

In a rabbit embryofetal developmental study, in which pregnant rabbits received tofacitinib during the period of organogenesis, tofacitinib was teratogenic at exposure levels approximately 13 times the recommended dose of 5 mg twice daily, and approximately 6.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3 times the recommended dose of 5 mg twice daily, and approximately 1.5 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in pregnant rabbits).

In a peri- and postnatal development study in pregnant rats that received tofacitinib from gestation day 6 through day 20 of lactation, there were reductions in live litter size, postnatal survival, and pup body weights at exposure levels approximately 73 times the recommended dose of 5 mg twice daily, and approximately 36 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 50 mg/kg/day in rats). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in

rats).

Lactation

Risk Summary
There are no data on the presence of tofacitinib in human milk, the effects on a breastfed infant, or the effects on milk production. Tofacitinib is present in the milk of lactating rats (see Data). When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adults treated with Tofacitinib, such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 18 hours after the last dose of Tofacitinib (approximately 6 elimination half-lives).

Data
Following administration of tofacitinib to lactating rats, concentrations of tofacitinib in milk over time paralleled those in serum, and were approximately 2 times higher in milk relative to maternal serum at all time points measured.

Females and Males of Reproductive Potential

Contraception

Females
In an animal reproduction study, tofacitinib at AUC multiples of 13 times the recommended dose of 5 mg twice daily and 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings (see section 4.6, sub-section Pregnancy). However, there is uncertainty as to how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential.

Infertility

Females
Based on findings in rats, treatment with Tofacitinib may result in reduced fertility in females of reproductive potential. It is not known if this effect is reversible (see section 6.1).

Geriatric Use

Of the 3315 patients who enrolled in rheumatoid arthritis 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 subjects 65 years of age and older was higher than among those under the age of 65.

Of the 1156 Tofacitinib treated patients in the UC program, a total of 77 patients (7%) were 65 years of age or older. The number of patients aged 65 years and older was not sufficient to determine whether they responded differently from younger patients.

As there is a higher incidence of infections in the elderly population in general, caution should be

used when treating the elderly (see section 4.4).

Use in Diabetics
As there is a higher incidence of infection in diabetic population in general, caution should be used when treating patients with diabetes.

Renal Impairment

Moderate and Severe Impairment
Tofacitinib treated patients with moderate or severe renal impairment had greater tofacitinib blood concentrations than Tofacitinib treated patients with normal renal function. Therefore, dosage adjustment of Tofacitinib is recommended in patients with moderate or severe renal impairment (including but not limited to those with severe insufficiency who are undergoing hemodialysis) (see section 4.2).

Mild Impairment
No dosage adjustment is required in patients with mild renal impairment.

Hepatic Impairment

Severe Impairment
Tofacitinib has not been studied in patients with severe hepatic impairment; therefore, use of Tofacitinib in patients with severe hepatic impairment is not recommended.

Moderate Impairment
Tofacitinib treated patients with moderate hepatic impairment had greater tofacitinib blood concentration than Tofacitinib-treated patients with normal hepatic function (see section 5.3). Higher blood concentrations may increase the risk of some adverse reactions. Therefore, dosage adjustment of Tofacitinib is recommended in patients with moderate hepatic impairment (see section 4.2).

Mild Impairment
No dosage adjustment of Tofacitinib is required in patients with mild hepatic impairment.

Hepatitis B or C Serology
The safety and efficacy of Tofacitinib have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following clinically significant adverse reactions are described elsewhere in the labeling:
- Serious Infections (see section 4.4)
- Mortality (see section 4.4)

- Malignancy and Lymphoproliferative Disorders (see section 4.4)
- Major Adverse Cardiovascular Events (see section 4.4)
- Thrombosis (see section 4.4)
- Gastrointestinal Perforations (see section 4.4)
- Hypersensitivity (see section 4.4)
- Laboratory Abnormalities (see section 4.4)

Clinical Trials Experience
Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Rheumatoid Arthritis
The clinical studies described in the following sections were conducted using tofacitinib. Although other doses of tofacitinib have been studied, the recommended dose of tofacitinib is 5 mg twice daily. In RA Safety Study 1, 1455 patients were treated with Tofacitinib 5 mg twice daily, 1456 patients were treated with 10 mg twice daily, and 1451 patients were treated with a TNF blocker for a median of 4.0 years (see section 5.2, Clinical Studies).

The following data includes two Phase 2 and five Phase 3 double-blind, placebo-controlled, multicenter trials. In these trials, patients were randomized to doses of tofacitinib 5 mg twice daily (292 patients) and 10 mg twice daily (306 patients) monotherapy, tofacitinib 5 mg twice daily (1044 patients) and 10 mg twice daily (1043 patients) in combination with DMARDs (including methotrexate) and placebo (809 patients). All seven placebo-controlled protocols included provisions for patients taking placebo to receive treatment with Tofacitinib at Month 3 or Month 6 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Therefore, some analyses that follow include patients who changed treatment by design or by patient response from placebo to tofacitinib in both the placebo and tofacitinib group of a given interval. Comparisons between placebo and tofacitinib were based on the first 3 months of exposure, and comparisons between tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily were based on the first 12 months of exposure.

The long-term safety population includes all patients who participated in a double-blind, placebo-controlled trial (including earlier development phase studies) and then participated in one of two long-term safety studies. The design of the long-term safety studies allowed for modification of tofacitinib doses according to clinical judgment. This limits the interpretation of the long-term safety data with respect to dose.

The most common serious adverse reactions were serious infections (see section 4.4).

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

Overall Infections
In the seven placebo-controlled trials, during the 0 to 3 months exposure, the overall frequency of infections was 20% and 22% in the 5 mg twice daily and 10 mg twice daily groups, respectively, and 18% in the placebo group.

The most commonly reported infections with tofacitinib were upper respiratory tract infections, nasopharyngitis, and urinary tract infections (4%, 3%, and 2% of patients, respectively).

Serious Infections
In the seven placebo-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 placebo-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).

Tuberculosis
In the seven placebo-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 placebo-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).

Opportunistic Infections (excluding tuberculosis)
In the seven placebo-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 placebo-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).

Malignancy

In the seven placebo-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 placebo-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).

Laboratory Abnormalities

Lymphopenia

In the controlled placebo-clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm^3 occurred in 0.04% of patients for the 5 mg twice daily and 10 mg twice daily Tofacitinib groups combined during the first 3 months of exposure.

Confirmed lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections (see section 4.4).

Neutropenia

In the placebo-controlled clinical trials, confirmed decreases in ANC below 1000 cells/mm^3 occurred in 0.07% of patients for the 5 mg twice daily and 10 mg twice daily Tofacitinib groups combined during the first 3 months of exposure.

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 placebo-controlled clinical trials (see section 4.4).

Liver Enzyme Elevations
Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were observed in patients treated with Tofacitinib. 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 placebo-controlled monotherapy trials (0-3 months), no differences in the incidence of ALT or AST elevations were observed between the placebo, and Tofacitinib 5 mg, and 10 mg twice daily groups.

In the placebo-controlled background DMARD trials (0-3 months), ALT elevations greater than 3x ULN were observed in 1.0%, 1.3% and 1.2% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. In these trials, AST elevations greater than 3x ULN were observed in 0.6%, 0.5% and 0.4% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively.

One case of drug-induced liver injury was reported in a patient treated with Tofacitinib 10 mg twice daily for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT greater than 3x ULN and bilirubin elevations greater than 2x ULN, which required hospitalizations and a liver biopsy.

Lipid Elevations
In the placebo-controlled clinical trials, dose-related elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were observed at one month of exposure and remained stable thereafter. Changes in lipid parameters during the first 3 months of exposure in the placebo-controlled clinical trials are summarized below:

- Mean LDL cholesterol increased by 15% in the Tofacitinib 5 mg twice daily arm and 19% in the Tofacitinib 10 mg twice daily arm.
- Mean HDL cholesterol increased by 10% in the Tofacitinib 5 mg twice daily arm and 12% in the Tofacitinib 10 mg twice daily arm.
- Mean LDL/HDL ratios were essentially unchanged in Tofacitinib -treated patients.

In a placebo-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 lipid parameters remained consistent with what was seen in the placebo-controlled clinical trials.

Serum Creatinine Elevations
In the placebo-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.

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 5 mg twice daily or 10 mg twice daily Tofacitinib and at least 1% greater than that observed in patients on placebo with or without DMARD are summarized in Table 4.

Table 4: Common Adverse Reactions* in Clinical Trials of Tofacitinib for the Treatment of Rheumatoid Arthritis with or without Concomitant DMARDs (0-3 Months)

	Tofacitinib 5 mg Twice Daily	**Tofacitinib 10 mg Twice Daily****	**Placebo**
Preferred Term	**N = 1336 (%)**	**N = 1349 (%)**	**N = 809 (%)**
Upper respiratory tract infection	4	4	3
Nasopharyngitis	4	3	3
Diarrhea	4	3	2
Headache	4	3	2
Hypertension	2	2	1

N reflects randomized and treated patients from the seven placebo-controlled clinical trials.
* reported in ≥2% of patients treated with either dose of tofacitinib and ≥1% greater than that reported for placebo.
** the recommended dose of tofacitinib for the treatment of rheumatoid arthritis is 5 mg twice daily (see section 4.2).

Other adverse reactions occurring in placebo-controlled and open-label extension studies included:

Blood and lymphatic system disorders: Anemia
Infections and infestations: Diverticulitis
Metabolism and nutrition disorders: Dehydration
Psychiatric disorders: Insomnia
Nervous system disorders: Paresthesia
Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion, interstitial lung disease (cases were limited to patients with rheumatoid arthritis and some were fatal)
Gastrointestinal disorders: Abdominal pain, dyspepsia, vomiting, gastritis, nausea
Hepatobiliary disorders: Hepatic steatosis
Skin and subcutaneous tissue disorders: Rash, erythema, pruritus
Musculoskeletal, connective tissue and bone disorders: Musculoskeletal pain, arthralgia,

tendonitis, joint swelling
Neoplasms benign, malignant and unspecified (including cysts and polyps): Non-melanoma skin cancers
General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema

Clinical Experience in Methotrexate-naïve Patients
Study RA-VI was an active-controlled clinical trial in methotrexate-naïve patients (see section 5.2). The safety experience in these patients was consistent with Studies RA-I through V.

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 (PsA). Although other doses of Tofacitinib have been studied, the recommended dose of Tofacitinib is 5 mg twice daily. A dosage of Tofacitinib 10 mg twice daily is not recommended for the treatment of PsA (see section 4.2).

Study PsA-I (NCT01877668) had a duration of 12 months and enrolled patients who had an inadequate response to a nonbiologic DMARD and who were naïve to treatment with a TNF blocker. Study PsA-I included a 3-month placebo-controlled period and also included adalimumab 40 mg subcutaneously once every 2 weeks for 12 months.

Study PsA-II (NCT01882439) had a duration of 6 months and enrolled patients who had an inadequate response to at least one approved TNF blocker. This clinical trial included a 3-month placebo-controlled period.

In these combined Phase 3 clinical trials, 238 patients were randomized and treated with Tofacitinib 5 mg twice daily and 236 patients were randomized and treated with Tofacitinib 10 mg twice daily. All patients in the clinical trials were required to receive treatment with a stable dose of a nonbiologic DMARD [the majority (79%) received methotrexate]. 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.

During the 2 PsA controlled clinical trials, there were 3 malignancies (excluding NMSC) in 474 patients receiving Tofacitinib plus non-biologic DMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus non-biologic DMARD group (3 months exposure) and 0 malignancies in 106 patients in the adalimumab plus non-biologic DMARD group (12 months exposure). No lymphomas were reported. Malignancies have also been observed in the long-term extension study in psoriatic arthritis patients treated with Tofacitinib.

The safety profile observed in patients with active psoriatic arthritis treated with Tofacitinib was consistent with the safety profile observed in rheumatoid arthritis patients.

Ankylosing Spondylitis
Tofacitinib 5 mg twice daily was studied in patients with active ankylosing spondylitis (AS) in a confirmatory double-blind placebo-controlled Phase 3 clinical trial (Study AS-I) and in a dose-ranging Phase 2 clinical trial (Study AS-II).

Study AS-I (NCT03502616) had a duration of 48 weeks and enrolled patients who had an inadequate response to at least 2 NSAIDs. Study AS-I included a 16-week double-blind period in which patients received Tofacitinib 5 mg or placebo twice daily and a 32-week open-label treatment period in which all patients received Tofacitinib 5 mg twice daily.

Study AS-II (NCT01786668) had a duration of 16 weeks and enrolled patients who had an inadequate response to at least 2 NSAIDs. This clinical trial included a 12-week treatment period in which patients received either Tofacitinib 2 mg, 5 mg, 10 mg, or placebo twice daily.

In the combined Phase 2 and Phase 3 clinical trials, a total of 420 patients were treated with either Tofacitinib 2 mg, 5 mg, or 10 mg twice daily. Of these, 316 patients were treated with Tofacitinib 5 mg twice daily for up to 48 weeks. In the combined double-blind period, 185 patients were randomized to and treated with Tofacitinib 5 mg twice daily and 187 to placebo for up to 16 weeks. Concomitant treatment with stable doses of nonbiologic DMARDs, NSAIDs, or corticosteroids (≤10 mg/day) was permitted. The study population randomized and treated with Tofacitinib included 13 (3.1%) patients aged 65 years or older and 18 (4.3%) patients with diabetes at baseline.

The safety profile observed in patients with AS treated with Tofacitinib was consistent with the safety profile observed in RA and PsA patients.

Ulcerative Colitis

Tofacitinib has been studied in patients with moderately to severely active UC in 4 randomized, double-blind, placebo-controlled trials (UC I, UC II, UC III, and dose ranging UC V) and an open-label long term extension study (UC IV) see section (5.2).

Adverse reactions reported in ≥5% of patients treated with either 5 mg or 10 mg twice daily of Tofacitinib and ≥1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

Induction Trials (Study UC-I, UC-II, and UC-V):
Common adverse reactions reported in ≥2% of patients treated with Tofacitinib 10 mg twice daily and ≥1% greater than that reported in patients receiving placebo in the 3 induction trials were: headache, nasopharyngitis, elevated cholesterol levels, acne, increased blood creatine phosphokinase, and pyrexia.

Maintenance Trial (Study UC-III)
Common adverse reactions reported in ≥4% of patients treated with either dose of Tofacitinib and ≥1% greater than reported in patients receiving placebo are shown in Table 5.

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

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

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

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

Dose-dependent adverse reactions seen in patients treated with Tofacitinib 10 mg twice daily, in comparison to 5 mg twice daily, include the following: herpes zoster infections, serious infections, and NMSC (see section 4.4).

During the UC controlled clinical studies (8-week induction and 52-week maintenance studies), which included 1220 patients, 0 cases of solid cancer or lymphoma were observed in Tofacitinib -treated patients.

In the long-term extension study, malignancies (including solid cancers, lymphomas and NMSC) were observed in patients treated with Tofacitinib 5 mg and 10 mg twice daily (see section 4.4). Five cases of pulmonary embolism were reported in patients taking Tofacitinib 10 mg twice daily, including one fatality in a patient with advanced cancer (see section 4.4).

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of Tofacitinib. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: Drug hypersensitivity (events such as angioedema and urticaria have been observed).

4.9 Overdose

There is no specific antidote for overdose with tofacitinib. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions.

In a study in subjects with end stage renal disease (ESRD) undergoing hemodialysis, plasma tofacitinib concentrations declined more rapidly during the period of hemodialysis and dialyzer efficiency, calculated as dialyzer clearance/blood flow entering the dialyzer, was high [mean (SD) = 0.73 (0.15)]. However, due to the significant non-renal clearance of tofacitinib, the fraction of total elimination occurring by hemodialysis was small, and thus limits the value of hemodialysis for treatment of overdose with Tofacitinib.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). Tofacitinib inhibited the *in vitro* activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC_{50} of 406, 56, and 1377 nM, respectively. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known.

5.2 Pharmacodynamic properties

Treatment with tofacitinib was associated with dose-dependent reductions of circulating CD16/56+ natural killer cells, with estimated maximum reductions occurring at approximately 8-10 weeks after initiation of therapy. These changes generally resolved within 2-6 weeks after discontinuation of treatment. Treatment with 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. The clinical significance of these changes is unknown.

Total serum IgG, IgM, and IgA levels after 6-month dosing in patients with rheumatoid arthritis were lower than placebo; however, changes were small and not dose-dependent.

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 pharmacokinetic 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 Studies - Rheumatoid Arthritis

The tofacitinib clinical development program included six confirmatory trials. Although other doses have been studied, the recommended dose of tofacitinib is 5 mg twice daily. A dosage of Tofacitinib 10 mg twice daily is not a recommended regimen for the treatment of rheumatoid arthritis (see section 4.2).

Confirmatory Trials

Study RA - I (NCT00814307) was a 6-month monotherapy trial in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic 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) less than 2.6.

Study RA - II (NCT00856544) was a 12-month trial in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a nonbiologic 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, nonresponding patients 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) less than 2.6 at month 6.

Study RA - III (NCT00853385) was a 12-month trial in 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 RA - IV (NCT00847613) was a 2-year trial 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 RA - V (NCT00960440) was a 6-month trial in which 399 patients with moderate to

severe active rheumatoid arthritis who had an inadequate response to at least one approved TNF-blocking 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) less than 2.6.

Study RA - VI (NCT01039688) was a 2-year monotherapy trial with a planned analysis at 1 year in which 952 MTX-naïve patients with moderate to severe active rheumatoid arthritis received tofacitinib 5 or 10 mg twice daily or MTX dose-titrated over 8 weeks to 20 mg weekly. The primary endpoints were mean change from baseline in van der Heijde-modified Total Sharp Score (mTSS) at Month 6 and the proportion of patients who achieved an ACR70 response at Month 6.

Clinical Response
The percentages of tofacitinib-treated patients achieving ACR20, ACR50, and ACR70 responses in Studies RA-I, IV, and V are shown in Table 6. Similar results were observed with Studies RA II and III. In trials RA I through -V, patients treated with 5 mg twice daily tofacitinib had higher ACR20, ACR50, and ACR70 response rates versus placebo, with or without background DMARD treatment, at Month 3 and Month 6. Higher ACR20 response rates were observed within 2 weeks compared to placebo. In the 12-month trials, ACR response rates in tofacitinib-treated patients were consistent at 6 and 12 months.

Table 6: Proportion of Patients with an ACR Response

	Percent of Patients							
	Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders[c]			**MTX Inadequate Responders[d]**			**TNF Blocker Inadequate Responders[e]**	
	Study I			**Study IV**			**Study V**	
N[a]	PBO 122	Tofacitinib 5 mg Twice Daily 243		PBO + MTX 160	Tofacitinib 5 mg Twice Daily + MTX 321		PBO + MTX 132	Tofacitinib 5 mg Twice Daily + MTX 133
ACR20 Month 3 Month 6	 26% NA[b]	 59% 69%		 27% 25%	 55% 50%		 24% NA	 41% 51%
ACR50 Month 3 Month 6	 12% NA	 31% 42%		 8% 9%	 29% 32%		 8% NA	 26% 37%
ACR70 Month 3 Month 6	 6% NA	 15% 22%		 3% 1%	 11% 14%		 2% NA	 14% 16%

[a] N is number of randomized and treated patients.
[b] NA Not applicable, as data for placebo treatment is not available beyond 3 months in Studies I and V due to placebo advancement.
[c] Inadequate response to at least one DMARD (biologic or nonbiologic) due to lack of efficacy or toxicity.

[d] Inadequate response to MTX defined as the presence of sufficient residual disease activity to meet the entry criteria.
[e] Inadequate response to a least one TNF blocker due to lack of efficacy and/or intolerance.

In Study RA-IV, a greater proportion of patients treated with tofacitinib 5 mg twice daily plus MTX achieved a low level of disease activity as measured by a DAS28-4(ESR) less than 2.6 at 6 months compared to those treated with MTX alone (Table 7).

Table 7: Proportion of Patients with DAS28-4(ESR) Less than 2.6 with Number of Residual Active Joints

Study IV		
DAS28-4(ESR) Less Than 2.6	**Placebo + MTX** **160**	**Tofacitinib 5 mg Twice Daily + MTX** **321**
Proportion of responders at Month 6 (n)	1% (2)	6% (19)
Of responders, proportion with 0 active joints (n)	50% (1)	42% (8)
Of responders, proportion with 1 active joint (n)	0	5% (1)
Of responders, proportion with 2 active joints (n)	0	32% (6)
Of responders, proportion with 3 or more active joints (n)	50% (1)	21% (4)

The results of the components of the ACR response criteria for Study RA-IV are shown in Table 8. Similar results were observed for Tofacitinib in Studies RA-I, II III, V, and VI.

Table 8: Components of ACR Response at Month 3

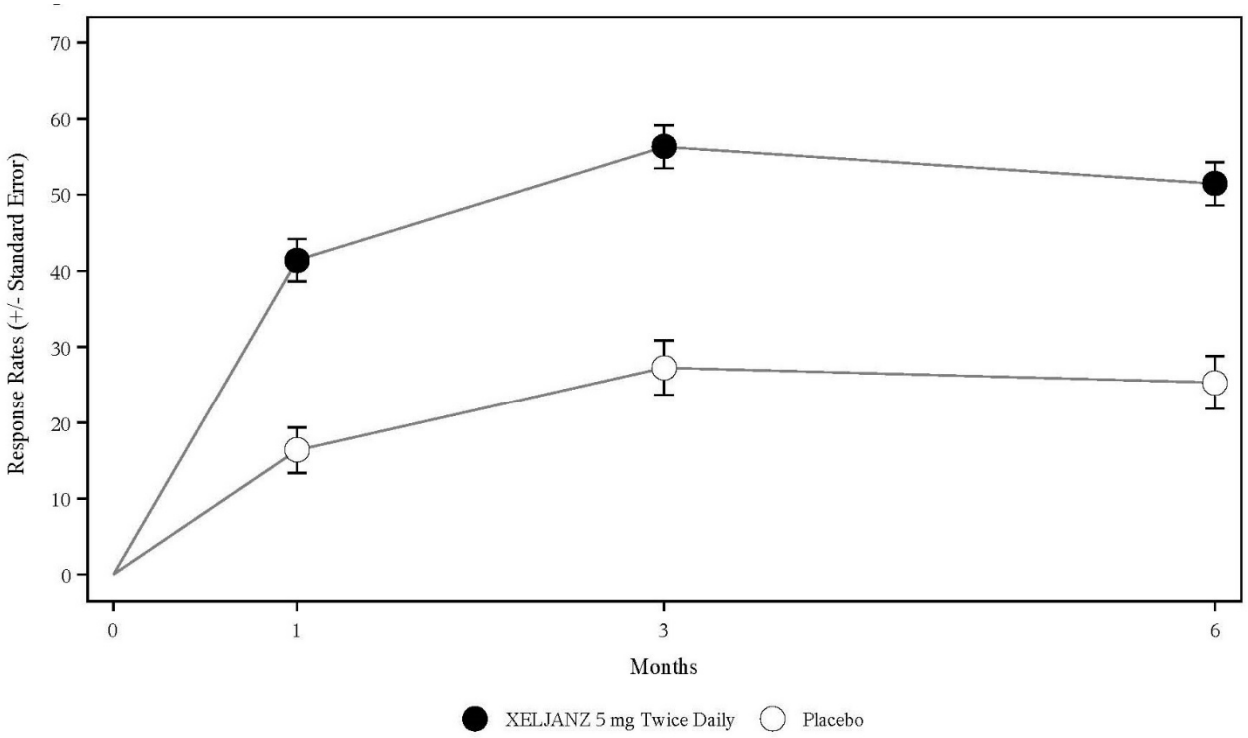
	Study IV			
	Tofacitinib 5 mg Twice Daily + MTX N=321		**Placebo + MTX N=160**	
Component (mean)[a]	Baseline	Month 3[a]	Baseline	Month 3[a]
Number of tender joints (0-68)	24 (14)	13 (14)	23 (13)	18 (14)
Number of swollen joints (0-66)	14 (8)	6 (8)	14 (9)	10 (9)
Pain[b]	58 (23)	34 (23)	55 (24)	47 (24)
Patient global assessment[b]	58 (24)	35 (23)	54 (23)	47 (24)
Disability index (HAQ-DI)[c]	1.41 (0.68)	0.99 (0.65)	1.32 (0.67)	1.19 (0.68)
Physician global assessment[b]	59 (16)	30 (19)	56 (18)	43 (22)
CRP (mg/L)	15.3 (19.0)	7.1 (19.1)	13.7 (14.9)	14.6 (18.7)

	Study IV	
	Tofacitinib 5 mg Twice Daily + MTX N=321	**Placebo + MTX N=160**

[a] Data shown is mean (Standard Deviation) at Month 3.
[b] Visual analog scale: 0 = best, 100 = worst.
[c] 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 RA-IV is shown in Figure 1. Similar responses were observed for tofacitinib in Studies RA-I, II, III, V, and VI.

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



Non-responder imputation was used. Patients who withdrew from the study were counted as failures, as were patients who failed to have at least a 20% improvement in joint counts at Month 3.

Radiographic response

Two studies were conducted to evaluate the effect of tofacitinib on structural joint damage. In Study RA-IV and Study RA-VI, progression of structural joint damage was assessed radiographically and expressed as change from baseline in mTSS and its components, the erosion score and joint space narrowing score, at Months 6 and 12. The proportion of patients with no radiographic progression (mTSS change less than or equal to 0) was also assessed.

In Study RA-IV, tofacitinib 5 mg twice daily reduced the mean progression of structural damage (not statistically significant). as shown in Table 9. Analyses of erosion and joint space narrowing scores were consistent with the overall results.

In the placebo plus MTX group, 74% of patients experienced no radiographic progression at Month 6 compared to 84% of patients treated with tofacitinib plus MTX 5 mg twice daily.

In Study RA-VI, tofacitinib monotherapy inhibited the progression of structural damage compared to MTX at Months 6 and 12 as shown in Table 9. Analyses of erosion and joint space narrowing scores were consistent with the overall results.

In the MTX group, 55% of patients experienced no radiographic progression at Month 6 compared to 73% of patients treated with tofacitinib 5 mg twice daily.

Table 9: Radiographic Changes at Months 6 and 12

	Study IV		
	Placebo **N=139** **Mean (SD)[a]**	**Tofacitinib 5 mg Twice Daily** **N=277** **Mean (SD)[a]**	**Tofacitinib 5 mg Twice Daily** **Mean Difference from Placebo[b] (CI)**
mTSS[c]			
Baseline	33 (42)	31 (48)	-
Month 6	0.5 (2.0)	0.1 (1.7)	-0.3 (-0.7, 0.0)
	Study VI		
	MTX **N=166** **Mean (SD)[a]**	**Tofacitinib 5 mg Twice Daily** **N=346** **Mean (SD)[a]**	**Tofacitinib 5 mg Twice Daily** **Mean Difference from MTX[b] (CI)**
mTSS[c]			
Baseline	17 (29)	20 (40)	-
Month 6	0.8 (2.7)	0.2 (2.3)	-0.7 (-1.0, -0.3)
Month 12	1.3 (3.7)	0.4 (3.0)	-0.9 (-1.4, -0.4)

[a] SD = Standard Deviation
[b] Difference between least squares means tofacitinib minus placebo or MTX (95% CI = 95% confidence interval)
[c] Month 6 and Month 12 data are mean change from baseline.

Physical Function Response

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving Tofacitinib 5 mg twice daily demonstrated greater improvement from baseline in physical functioning compared to placebo at Month 3.

The mean (95% CI) difference from placebo in HAQ-DI improvement from baseline at Month 3 in Study RA-III was -0.22 (-0.35, -0.10) in patients receiving 5 mg Tofacitinib twice daily. Similar results were obtained in Studies RA-I, II, IV and V. In the 12-month trials, HAQ-DI results in tofacitinib-treated patients were consistent at 6 and 12 months.

Other Health Related Outcomes

General health status was assessed by the Short Form health survey (SF-36). In Studies RA-I, IV, and V, patients receiving Tofacitinib 5 mg twice daily demonstrated 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.

Psoriatic Arthritis

The Tofacitinib clinical development program to assess efficacy and safety included 2 multicenter, randomized, double-blind, placebo-controlled confirmatory trials in 816 patients 18 years of age and older (PsA-I and PsA-II). Although other doses have been studied, the recommended dose of Tofacitinib is 5 mg twice daily. Tofacitinib 10 mg twice daily is not recommended for the treatment of psoriatic arthritis (see section 4.2). All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender/painful joints and at least 3 swollen joints, and active plaque psoriasis. Patients randomized and treated across the 2 clinical trials represented different psoriatic arthritis subtypes at screening, including <5 joints or asymmetric involvement (21%), ≥5 joints involved (90%), distal interphalangeal (DIP) joint involvement (61%), arthritis mutilans (8%), and spondylitis (19%). Patients in these clinical trials had a diagnosis of psoriatic arthritis for a mean (SD) of 7.7 (7.2) years. At baseline, 80% and 53% of patients had enthesitis and dactylitis, respectively. At baseline, all patients were required to receive treatment with a stable dose of a nonbiologic DMARD (79% received methotrexate, 13% received sulfasalazine, 7% received leflunomide, 1% received other nonbiologic DMARDs). In both clinical trials, the primary endpoints were the ACR20 response and the change from baseline in HAQ-DI at Month 3.

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

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

Clinical Response

At Month 3, patients treated with Tofacitinib 5 mg twice daily had higher ($p \leq 0.05$) response rates versus placebo for ACR20, ACR50, and ACR70 in Study PsA-I and for ACR20 and ACR50 in Study PsA-II; ACR70 response rates were also higher for Tofacitinib 5 mg twice daily versus placebo in Study PsA-II, although the differences versus placebo were not statistically significant ($p > 0.05$) (Tables 10 and 11).

Table 10: Proportion of Patients with an ACR Response in Study PsA-I* [Nonbiologic DMARD Inadequate Responders (TNF Blocker-Naïve)]

Treatment Group	Placebo	Tofacitinib 5 mg Twice Daily	
N[a]	105	107	
	Response Rate	Response Rate	Difference (%) 95% CI from Placebo
Month 3			
ACR20	33%	50%	17.1 (4.1, 30.2)
ACR50	10%	28%	18.5 (8.3, 28.7)
ACR70	5%	17%	12.1 (3.9, 20.2)

Subjects with missing data were treated as non-responders.
* Subjects received one concomitant nonbiologic DMARD.
[a] N is number of randomized and treated patients.

Table 11: Proportion of Patients with an ACR Response in Study PsA-II* (TNF Blocker Inadequate Responders)

Treatment Group	Placebo	Tofacitinib 5 mg Twice Daily	
N[a]	131	131	
	Response Rate	Response Rate	Difference (%) 95% CI from Placebo
Month 3			
ACR20	24%	50%	26.0 (14.7, 37.2)
ACR50	15%	30%	15.3 (5.4, 25.2)
ACR70	10%	17%	6.9 (-1.3, 15.1)

Subjects with missing data were treated as non-responders.
* Subjects received one concomitant nonbiologic DMARD.
[a] N is number of randomized and treated patients.

Improvements from baseline in the ACR response criteria components for both studies are shown in Table 12.

Table 12: Components of ACR Response at Baseline and Month 3 in Studies PsA-I and PsA-II

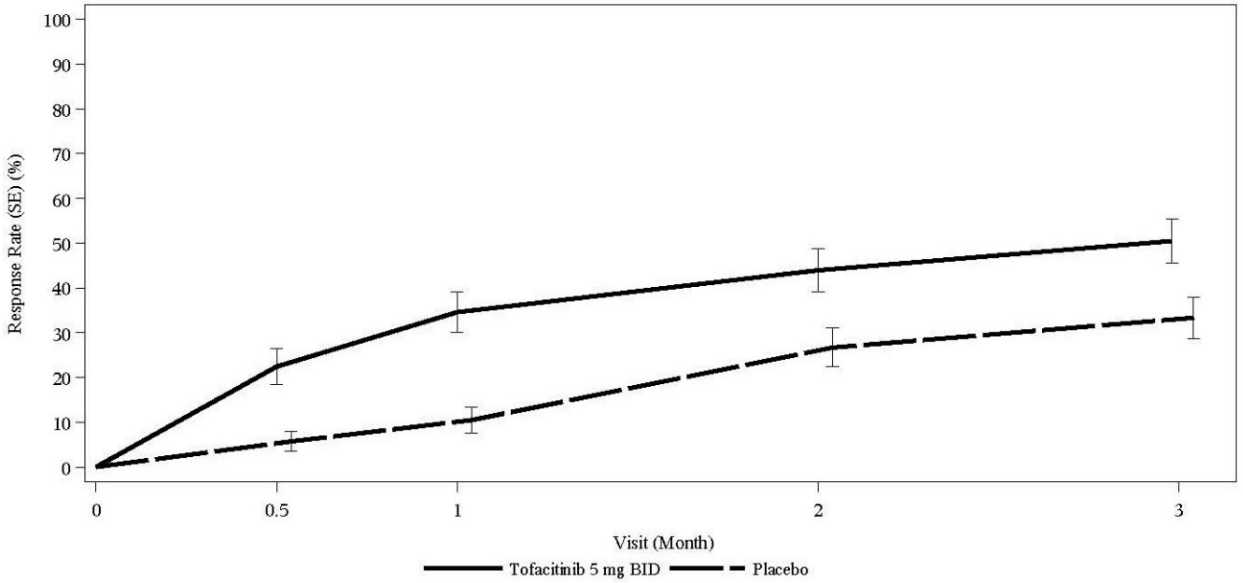
	Nonbiologic DMARD Inadequate Responders (TNF Blocker-Naïve)		TNF Blocker Inadequate Responders	
	Study PsA-I*		Study PsA-II*	
Treatment Group	Placebo	Tofacitinib 5 mg Twice Daily	Placebo	Tofacitinib 5 mg Twice Daily
N at Baseline	105	107	131	131
ACR Component[a]				
Number of tender/painful joints (0-68)				
Baseline	20.6	20.5	19.8	20.5
Month 3	14.6	12.2	15.1	11.5

Number of swollen joints (0-66) Baseline Month 3	 11.5 7.1	 12.9 6.3	 10.5 7.7	 12.1 4.8
Patient assessment of arthritis pain[b] Baseline Month 3	 53.2 44.7	 55.7 34.7	 54.9 48.0	 56.4 36.1
Patient global assessment of arthritis[b] Baseline Month 3	 53.9 44.4	 54.7 35.5	 55.8 49.2	 57.4 36.9
HAQ-DI[c] Baseline Month 3	 1.11 0.95	 1.16 0.81	 1.25 1.09	 1.26 0.88
Physician's Global Assessment of Arthritis[b] Baseline Month 3	 53.8 35.4	 54.6 29.5	 53.7 36.4	 53.5 27.0
CRP (mg/L) Baseline Month 3	 10.4 8.6	 10.5 4.0	 12.1 11.4	 13.8 7.7

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

The percentage of ACR20 responders by visit for Study PsA-I is shown in Figure 2. Similar responses were observed in Study PsA-II. In both studies, improvement in ACR20 response on Tofacitinib was observed at the first visit after baseline (Week 2).

Figure 2: Percentage of ACR20 Responders by Visit Through Month 3 in Study PsA-I*



BID=twice daily; SE=standard error.
Subjects with missing data were treated as non-responders.
* Subjects received one concomitant nonbiologic DMARD.

In patients with active psoriatic arthritis evidence of benefit in enthesitis and dactylitis was observed with Tofacitinib treatment.

Physical Function

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving Tofacitinib 5 mg twice daily demonstrated significantly greater improvement ($p \leq 0.05$) from baseline in physical functioning compared to placebo at Month 3 (Table 13).

Table 13: Change from Baseline in HAQ-DI in Studies PsA-I and PsA-II

	Least Squares Mean Change from Baseline In HAQ-DI at Month 3			
	Nonbiologic DMARD Inadequate Responders[b] (TNF Blocker-Naïve)		**TNF Blocker Inadequate Responders[c]**	
	Study PsA-I*		**Study PsA-II***	
Treatment Group	Placebo	Tofacitinib 5 mg Twice Daily	Placebo	Tofacitinib 5 mg Twice Daily
N[a]	104	107	131	129
LSM Change from Baseline	-0.18	-0.35	-0.14	-0.39
Difference from Placebo (95% CI)	-	-0.17 (-0.29, -0.05)	-	-0.25 (-0.38, -0.13)

* Subjects received one concomitant nonbiologic DMARD.
[a] N is the total number of subjects in the statistical analysis.
[b] Inadequate response to at least one nonbiologic DMARD due to lack of efficacy and/or intolerability.
[c] Inadequate response to at least one TNF blocker due to lack of efficacy and/or intolerability.

In Study PsA-I, the HAQ-DI responder rate (response defined as having improvement from baseline of ≥0.35) at Month 3 was 53% in patients receiving Tofacitinib 5 mg twice daily and 31% in patients receiving placebo. Similar responses were observed in Study PsA-II.

Other Health-Related Outcomes
General health status was assessed by the Short Form health survey (SF-36). In Studies PsA-I and PsA-II, patients receiving Tofacitinib 5 mg twice daily had greater improvement from baseline compared to placebo in Physical Component Summary (PCS) score, but not in Mental Component Summary (MCS) score at Month 3. Patients receiving Tofacitinib 5 mg twice daily reported consistently greater improvement relative to placebo in the domains of Physical Functioning, Bodily Pain, Vitality, and Social Functioning, but not in Role-Physical, General Health, Role-Emotional, or Mental Health.

Radiographic Response
Treatment effect on inhibition of radiographic progression in psoriatic arthritis could not be established from the results of Study PsA-I.

Ankylosing Spondylitis
The Tofacitinib clinical development program to assess the efficacy and safety included one placebo-controlled confirmatory trial (Study AS-I). Patients had active disease as defined by both Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and back pain score (BASDAI question 2) of greater or equal to 4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease modifying anti-rheumatic drug (DMARD) therapy.

Confirmatory Trial (Study AS-I)
Study AS-I was a randomized, double-blind, placebo-controlled, 48-week clinical trial in 269 adult patients who had an inadequate response (inadequate clinical response or intolerance) to at least 2 NSAIDs. Patients were randomized and treated with Tofacitinib 5 mg twice daily or placebo for 16 weeks of blinded treatment and then all received treatment of Tofacitinib 5 mg twice daily for additional 32 weeks. The primary endpoint was to evaluate the proportion of patients who achieved an ASAS20 response at Week 16.

Approximately 7% and 21% of patients used concomitant methotrexate or sulfasalazine, respectively from baseline to Week 16. Twenty-two percent of patients had an inadequate response to 1 or 2 TNF blockers.

Clinical Response
Patients treated with Tofacitinib 5 mg twice daily achieved greater improvements in ASAS20 and ASAS40 responses compared to placebo at Week 16 (Table 14). Consistent results were observed in the subgroup of patients who had an inadequate response to TNF blockers for both the ASAS20 (primary endpoint) and ASAS40 (secondary endpoint) at Week 16 (Table 14).

Table 14: ASAS20 and ASAS40 Responses at Week 16, Study AS-I

	Placebo	Tofacitinib 5 mg Twice Daily	Difference from Placebo (95% CI)
All patients (N)	N=136	N=133	
ASAS20 response*, %	29	56	27 (16, 38)**
ASAS40 response*, %	13	41	28 (18, 38) **
TNFi-IR patients (N)	N=30	N=29	
ASAS20 response, %	17	41	25 (2, 47)
ASAS40 response, %	7	28	21 (2, 39)

* type I error-controlled.
** p-value <0.0001.
Abbreviations: CI = confidence interval; TNFi-IR = tumor necrosis factor inhibitor inadequate response.

The improvements in the components of the ASAS response and other measures of disease activity were higher in Tofacitinib 5 mg twice daily compared to placebo as shown in Table 15.

Table 15: ASAS Components and Other Measures of Disease Activity at Week 16, Study AS-I

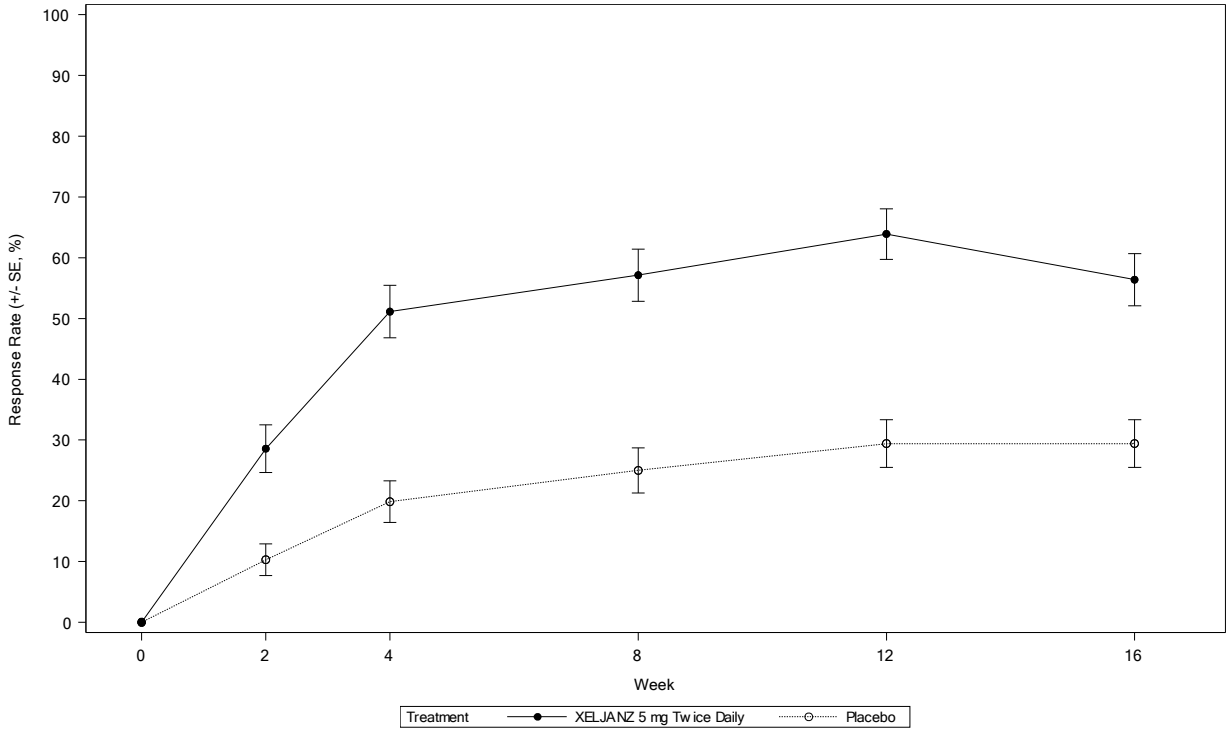
	Placebo (N=136)		Tofacitinib 5 mg Twice Daily (N=133)		
	Baseline (mean)	Week 16 (LSM change from Baseline)g	Baseline (mean)	Week 16 (LSM change from Baseline)g	Difference from Placebo (95% CI)g
ASAS Components					
Patient Global Assessment of Disease Activity (0-10)a,*	7.0	-1.0	6.9	-2.5	-1.5 (-2.00, -0.97)**
Total spinal pain (0-10)a,*	6.9	-1.1	6.9	-2.6	-1.5 (-2.00, -1.03)**
BASFI (0-10)b,*	5.9	-0.8	5.8	-2.0	-1.2 (-1.64, -0.79)**
Inflammation (0-10)c,*	6.8	-1.1	6.6	-2.8	-1.7 (-2.13, -1.18)**

	Placebo (N=136)		Tofacitinib 5 mg Twice Daily (N=133)		
	Baseline (mean)	**Week 16 (LSM change from Baseline)[g]**	**Baseline (mean)**	**Week 16 (LSM change from Baseline)[g]**	**Difference from Placebo (95% CI)[g]**
BASDAI Scored	6.5	-1.2	6.4	-2.6	-1.4 (-1.86, -0.98)**
BASMIe,*	4.4	-0.1	4.5	-0.6	-0.5 (-0.66, -0.36)**
hsCRPf,* (mg/dL)	1.8	-0.1	1.6	-1.1	-0.9 (-1.17, -0.69)**

* type I error-controlled.
** $p < 0.0001$.
[a] Measured on a numerical rating scale with 0 = not active or no pain, 10 = very active or most severe pain.
[b] Bath Ankylosing Spondylitis Functional Index measured on a numerical rating scale with 0 = easy and 10 = impossible.
[c] Inflammation is the mean of two patient-reported stiffness self-assessments in BASDAI.
[d] Bath Ankylosing Spondylitis Disease Activity Index total score.
[e] Bath Ankylosing Spondylitis Metrology Index.
[f] High sensitivity C-reactive protein.
[g] Estimates are generated based on a mixed model for repeated measures using both on-treatment and off-treatment data.
LSM = least squares mean.

The percentage of patients achieving ASAS20 response by visit is shown in Figure 3.

Figure 3: ASAS20 Response Over Time Up to Week 16, Study AS-I



SE=standard error.
Patients with missing data were treated as non-responders.

Other Health-Related Outcomes
Patients treated with Tofacitinib 5 mg twice daily achieved greater improvements from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) (-4.0 vs -2.0) compared to placebo-treated patients at Week 16.

Ulcerative Colitis
Induction Trials (Study UC-I [NCT01465763] and Study UC-II [NCT01458951])
In two identical induction trials (UC-I and UC-II), 1139 patients were randomized (598 and 541 patients, respectively) to Tofacitinib 10 mg twice daily or placebo with a 4:1 treatment allocation ratio. These trials included adult patients with moderately to severely active UC (total Mayo score of 6 to 12, with an endoscopy subscore of at least 2, and rectal bleeding subscore of at least 1) and who had failed or were intolerant to at least 1 of the following treatments: oral or intravenous corticosteroids, azathioprine, 6-MP or TNF blocker. Tofacitinib is indicated for patients who have an inadequate response and intolerance to one or more TNF blockers (see section 4.1).

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

Patients were permitted to use stable doses of oral aminosalicylates and corticosteroids (prednisone daily dose up to 25 mg equivalent). Concomitant immunosuppressants (oral immunomodulators or biologic therapies) were not permitted for UC patients during these studies.

A total of 52%, 73% and 72% of patients had previously failed or were intolerant to TNF blockers (51% in Study UC-1 and 52% in Study UC-II), corticosteroids (75% in Study UC I and 71% in Study UC II), and/or immunosuppressants (74% in Study UC I and 70% in Study UC II), respectively.

Oral corticosteroids were received as concomitant treatment for UC by 47% of patients (45% in Study UC-I and 48% in Study UC-II) and 71% were receiving concomitant aminosalicylates as treatment for UC (71% in Study UC-I, and 72% in Study UC-II). The baseline clinical characteristics were generally similar between the Tofacitinib treated patients and patients receiving placebo.

The primary endpoint of Study UC-I and Study UC-II 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.

The efficacy results of Study UC-I and Study UC-II based on the centrally read endoscopy results are shown in Table 16.

Table 16: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 8 (Induction Study UC-I and Study UC-II, Central Endoscopy Read)

Study UC-I			
Endpoint	**Placebo**	**Tofacitinib 10 mg Twice Daily**	**Treatment Difference versus Placebo (95% CI)**
Remission at Week 8[a]			
Total Population	N=122 8%	N=476 18%	10%* (4.3, 16.3)
With Prior TNF Blocker Failure[b]	N=64 2%	N=243 11%	
Without Prior TNF Blocker Failure[c]	N=58 16%	N=233 26%	
Improvement of endoscopic appearance of the mucosa at Week 8[d]			
Total Population	N=122 16%	N=476 31%	16%** (8.1, 23.4)
With Prior TNF Blocker Failure[b]	N=64 6%	N=243 23%	
Without Prior TNF Blocker Failure[c]	N=58 26%	N=233 40%	
Study UC-II			
Endpoint	**Placebo**	**Tofacitinib 10 mg Twice Daily**	**Treatment Difference (95% CI)**
Remission at Week 8[a]			
Total Population	N=112 4%	N=429 17%	13%** (8.1, 17.9)
With Prior TNF Blocker Failure[b]	N=60 0%	N=222 12%	
Without Prior TNF Blocker Failure[c]	N=52 8%	N=207 22%	
Improvement of endoscopic appearance of the mucosa at Week 8[d]			
Total Population	N=112 12%	N-429 28%	17%** (9.5, 24.1)
With Prior TNF Blocker Failure[b]	N=60 7%	N=222 22%	

Without Prior TNF Blocker Failure[c]	N=52 17%	N=207 36%	

* p-value <0.01, ** p-value <0.001.
CI = Confidence interval; N = number of patients in the analysis set; TNF = tumor necrosis factor
[a] Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.
[b] Prior TNF blocker failure was defined in this program as inadequate response, loss of response, or intolerance to TNF blocker therapy.
[c] Patients in this group had failed one or more conventional therapies (corticosteroid, azathioprine, 6-mercaptopurine) but did not have history of prior failure of TNF blocker therapy.
[d] Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).

Clinical Response at Week 8
Clinical response was defined as a decrease from baseline in Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the subscore for rectal bleeding of ≥1 point or absolute subscore for rectal bleeding of 0 or 1.

Clinical response was observed in 60% of patients treated with Tofacitinib 10 mg twice daily compared to 33% of placebo patients in Study UC-I and 55% compared to 29% in Study UC-II.

Normalization of the Endoscopic Appearance of the Mucosa at Week 8
Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0 and was observed in 7% of patients treated with Tofacitinib 10 mg twice daily compared to 2% of placebo patients in both Studies UC-I and UC-II.

Rectal Bleeding and Stool Frequency
Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in patients treated with Tofacitinib.

Maintenance Trial (Study UC-III [NCT01458574])
A total of 593 patients who completed the induction trials (UC-I or UC-II) and achieved clinical response were re-randomized with 1:1:1 treatment allocation ratio to Tofacitinib 5 mg twice daily, Tofacitinib 10 mg twice daily, or placebo for 52 weeks in Study UC-III. Tofacitinib 5 mg twice daily is the recommended dosage for maintenance therapy; limit use of Tofacitinib 10 mg twice daily beyond induction to those with loss of response and should be used for the shortest duration (see section 4.2). As in the induction trials, patients were permitted to use stable doses of oral aminosalicylates; however, corticosteroid tapering was required upon entrance into this study for patients who were receiving corticosteroids at baseline. Concomitant immunosuppressants (oral immunomodulators or biologic therapies) were not permitted.

At baseline of Study UC-III:

- 179 (30%) patients were in remission
- 289 (49%) patients were receiving oral corticosteroids
- 265 (45%), 445 (75%), and 413 (70%) patients had previously failed or were intolerant to TNF blocker therapy, corticosteroids, and immunosuppressants, respectively.

The primary endpoint was the proportion of patients in remission at Week 52. There were 2 key secondary endpoints: 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 Study UC III.

The efficacy results of Study UC-III based on the centrally read endoscopy results are summarized in Table 17.

Table 17: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints in Maintenance Study UC III (Central Endoscopy Read)

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

				Treatment Difference versus Placebo (95% CI)	
Endpoint	**Placebo**	**Tofacitinib 5 mg Twice Daily**	**Tofacitinib 10 mg Twice Daily**	**Tofacitinib 5 mg Twice Daily**	**Tofacitinib 10 mg Twice Daily**

***** p-value <0.0001.
CI = Confidence interval; N = number of patients in the analysis set; TNF = tumor necrosis factor.
[a] Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.
[b] Prior TNF blocker failure was defined in this program as inadequate response, loss of response, or intolerance to TNF blocker therapy.
[c] Patients in this group had failed one or more conventional therapies (corticosteroid, azathioprine, 6-mercaptopurine) but did not have history of prior failure of TNF blocker therapy.
[d] Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).
[e] Sustained corticosteroid-free remission was defined as being in remission and not taking corticosteroids for at least 4 weeks prior to the visit at both Week 24 and Week 52.

Maintenance of Clinical Response
Maintenance of clinical response was defined as the proportion of patients who met the definition of clinical response (defined as a decrease from the induction study (UC-I, UC-II) 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) at both Baseline and Week 52 of Study UC-III.

Maintenance of clinical response was observed in 52% in the Tofacitinib 5 mg twice daily group and 62% in the Tofacitinib 10 mg twice daily group compared to 20% of placebo patients.

Maintenance of Remission (Among Patients in Remission at Baseline)
In the 179 patients who were in remission at baseline of Study UC III (N = 59 for placebo, N = 65 for Tofacitinib 5 mg twice daily, N = 55 for Tofacitinib 10 mg twice daily), 46% in the Tofacitinib 5 mg twice daily group and 56% in the Tofacitinib 10 mg twice daily group maintained remission at Week 52 compared to 10% of placebo patients.

Normalization of the Endoscopic Appearance of the Mucosa
Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0 and was observed at Week 52 in 15% of patients in the Tofacitinib 5 mg twice daily group and 17% of patients in the Tofacitinib 10 mg twice daily group compared to 4% of placebo patients.

Open-label Extension Study (Study UC-IV [NCT01470612])
In Study UC-IV, 914 patients were treated of which 156 received 5 mg twice daily and 758 received 10 mg twice daily.

Of the 905 patients who were assigned to Tofacitinib 10 mg twice daily in the 8-week induction studies (Study UC-I or Study UC-II), 322 patients completed the induction studies but did not achieve clinical response. Of these 322 patients, 291 continued to receive Tofacitinib 10 mg twice daily (unblinded) and had available data after an additional 8 weeks in Study UC-IV. After 8 additional weeks (a total of 16 weeks treatment), 148 patients achieved clinical response, and

25 patients achieved remission (based on central endoscopy read). Among those 143 patients who achieved clinical response by 16 weeks and had available data at Week 52, 66 patients achieved remission (based on local endoscopy read) after continued treatment with Tofacitinib 10 mg twice daily for 52 weeks.

Safety Study

A randomized open-label trial (RA Safety Study 1; NCT02092467) was conducted to evaluate safety with Tofacitinib at two doses, 5 mg twice daily (N=1455) and 10 mg twice daily (N=1456), versus the TNF-blocker control (N=1451) in RA patients 50 years of age and older with at least one cardiovascular risk factor. The co-primary endpoints were adjudicated MACE (defined as cardiovascular death, non-fatal MI, and non-fatal stroke) and adjudicated malignancy (excluding non-melanoma skin cancer); the study was designed to exclude a prespecified risk margin of 1.8 for the hazard ratio of combined Tofacitinib regimens versus the TNF-blocker control for each co-primary endpoint. An independent committee conducted a blinded evaluation of the co-primary endpoints according to predefined criteria (adjudication). The study was event driven and patients were followed until a sufficient number of primary outcome events accrued. Other endpoints included mortality, serious infections, and thromboembolic events. The median on-study follow-up time was 4.0 years.

The mean age of the population was 61 years (range: 50 to 88 years). Most patients were female (78%) and Caucasian (77%). Patients had a diagnosis of RA for a mean of 10 years, and a median swollen and tender joint count of 11 and 15 respectively. Cardiovascular risk factors included cigarette smoking (current or past) (48%), hypertension (66%), high density lipoprotein < 40 mg/dL (12%), diabetes mellitus (17%), family history of premature coronary heart disease (15%), extra-articular disease associated with RA (37%), and history of coronary artery disease (11%).

The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNF blockers since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8 (for MACE, the upper limit of the 95% CI was 1.94; for malignancies excluding NMSC, the upper limit of the 95% CI was 2.09).

Table 18 shows the study results for each of the co-primary endpoints, and other endpoints. There was an increased risk of death, MACE, malignancies, serious infections, and thromboembolic events associated with both doses of Tofacitinib.

Table 18: Results of RA Safety Study 1

Endpoint	Tofacitinib 5 mg Twice Daily N=1455 PY=5490	Tofacitinib 10 mg Twice Daily N=1456 PY=5298	TNF Blocker N=1451 PY=5468
MACE, n [IR]	50 [0.91]	59 [1.11]	43 [0.79]
HR (95% CI)*	1.16 (0.77, 1.74)	1.41 (0.95, 2.10)	
MI,† n [IR]	20 [0.36]	21 [0.39]	11 [0.20]
HR (95% CI)*	1.81 (0.87, 3.79)	1.97 (0.95, 4.09)	

Endpoint	Tofacitinib 5 mg Twice Daily N=1455 PY=5490	Tofacitinib 10 mg Twice Daily N=1456 PY=5298	TNF Blocker N=1451 PY=5468
Stroke,† n [IR] HR (95% CI)*	18 [0.33] 0.89 (0.47, 1.69)	21 [0.39] 1.08 (0.59, 2.00)	20 [0.36]
Cardiovascular Death, n [IR] HR (95% CI)*	18 [0.32] 1.20 (0.60, 2.37)	25 [0.47] 1.71 (0.90, 3.24)	15 [0.27]
Malignancies Excl. NMSC, n [IR] HR (95% CI)*	62 [1.13] 1.47 (1.00, 2.18)	60 [1.13] 1.48 (1.00, 2.19)	42 [0.77]
Malignancies Excl. NMSC (among current and past smokers)††	41 [1.53]	48 [1.91]	25 [0.99]
HR (95% CI)*	1.55 (0.94, 2.55)	1.94 (1.19, 3.14)	
All Death HR (95% CI)*	49 [0.88] 1.29 (0.84, 1.96)	66 [1.23] 1.79 (1.20, 2.66)	38 [0.69]
Serious Infections HR (95% CI)*	155 [2.95] 1.17 (0.93, 1.47)	184 [3.65] 1.44 (1.15, 1.80)	133 [2.52]
DVT HR (95% CI)*	12 [0.22] 1.33 (0.56, 3.15)	15 [0.28] 1.72 (0.75, 3.92)	9 [0.16]
PE HR (95% CI)*	10 [0.18] 3.32 (0.91, 12.08)	26 [0.49] 8.95 (2.71, 29.56)	3 [0.05]
VTE HR (95% CI)*	18 [0.33] 1.50 (0.72, 3.10)	36 [0.68] 3.10 (1.61, 5.96)	12 [0.22]
ATE HR (95% CI)*	51 [0.93] 1.13 (0.76, 1.69)	55 [1.04] 1.26 (0.85, 1.87)	45 [0.83]
TE HR (95% CI)*	67 [1.23] 1.19 (0.84, 1.70)	86 [1.65] 1.60 (1.14, 2.23)	56 [1.03]

Note: Tofacitinib 10 mg twice daily was discontinued by the Data Monitoring Committee due to safety concerns, and ongoing patients switched from Tofacitinib 10 mg to Tofacitinib 5 mg. The column "Tofacitinib 10 mg Twice Daily" includes all events and follow-up for patients randomized to Tofacitinib 10 mg twice daily. A Tofacitinib 10 mg twice daily dosage is not recommended for the treatment of RA or PsA (see section 4.2).
N indicates number of patients; n indicates number of patients with events.
IR indicates incidence rate per 100 person-year (PY).
†MI and Stroke include fatal and non-fatal events.
††Data and analyses for Malignancies excluding NMSC for current and ex-smokers are included. There were 720 current and ex-smokers randomized to Tofacitinib 5 mg, 704 to Tofacitinib 10 mg, and 679 to TNF blockers.
*HR (95%) CI for Tofacitinib vs. TNF Blocker (Univariate Cox Proportional Hazard Model).
NMSC: Non-melanoma Skin Cancer; MACE: Major Adverse Cardiac Events; HR: Hazard Ratio; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolism; VTE: Venous Thromboembolism, first occurrence of a VTE, defined as the composite of adjudicated DVT and adjudicated PE; ATE: Arterial Thromboembolism; TE: Thromboembolism, first occurrence of a TE, defined as the composite of adjudicated VTE and unadjudicated ATE.

Lymphomas and lung cancers, which are a subset of all malignancies in RA Safety Study 1, were observed at a higher rate in patients treated with Tofacitinib 5 mg twice a day and Tofacitinib 10 mg twice a day compared to those treated with TNF blockers. Lymphoma was reported for 4 patients receiving Tofacitinib 5 mg twice a day, 6 patients receiving Tofacitinib 10 mg twice a day, and 1 patient receiving TNF blockers (Incidence Rate [IR] of 0.07, 0.11, and 0.02 per 100 patient-years, respectively). Among current and past smokers, lung cancer was reported for 13 patients receiving Tofacitinib 5 mg twice a day, 15 patients receiving Tofacitinib 10 mg twice

a day, and 7 patients receiving TNF blockers (IR of 0.48, 0.59, and 0.27 per 100 patient-years, respectively).

A Tofacitinib 10 mg twice daily dosage is not recommended for the treatment of RA or PsA or AS (see section 4.2).

5.3 Pharmacokinetic properties

Following oral administration of tofacitinib, peak plasma concentrations are reached within 0.5-1 hour, elimination half-life is about 3 hours and a dose-proportional increases in systemic exposure was observed in the therapeutic dose range. Steady-state concentrations are achieved in 24-48 hours with negligible accumulation after twice daily administration.

Table 19: Pharmacokinetic Parameters of Tofacitinib Following Multiple Oral Dosing

PK Parameters[a] (CV%)	Tofacitinib
Dosing Regimen	5 mg Twice Daily
AUC_{24} (ng.h/mL)	263.4 (15)
C_{max} (ng/mL)	42.7 (26)
C_{min} (ng/mL)	1.41 (40)
T_{max} (hours)	1.0 (0.5 to 14.0[b])

[a] Values represent the geometric mean, except T_{max}, for which is the median (range) is shown.
Abbreviations: AUC_{24} = area under the concentration-time profile from time 0 to 24 hours; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; T_{max} = time to C_{max}; CV = Coefficient of variation.
[b] Values beyond 12 hours were after the evening dose which was administered 12 hours after the morning dose of twice-daily Tofacitinib

Absorption

The absolute oral bioavailability of Tofacitinib is 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 meals (see section 4.2).

Distribution

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

Metabolism and Excretion

Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged drug, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of tofacitinib is attributed to parent molecule.

Pharmacokinetics in Patient Populations

Population pharmacokinetic analyses indicated that pharmacokinetic characteristics were similar between patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and UC. The coefficient of variation (%) in AUC of tofacitinib were generally similar across different disease patients, ranging from 22% to 34% (Table 20).

Table 20. Tofacitinib Exposure in Patient Populations at 5 mg and 10 mg Twice Daily Doses

Pharmacokinetic Parameters[a] Geometric Mean (CV%)	Tofacitinib 5 mg Twice Daily				Tofacitinib 10 mg Twice Daily
	Rheumatoid Arthritis	Psoriatic Arthritis	Ankylosing Spondylitis	Ulcerative Colitis	Ulcerative Colitis
$AUC_{0\text{-}24,\ ss}$ (ng·h/mL)	504 (22.0%)	419 (34.1%)	381 (25.4%)	423 (22.6%)	807 (24.6%)

Abbreviations: $AUC_{0\text{-}24,\ ss}$=area under the plasma concentration-time curve over 24 hours at steady state; CV=coefficient of variation.

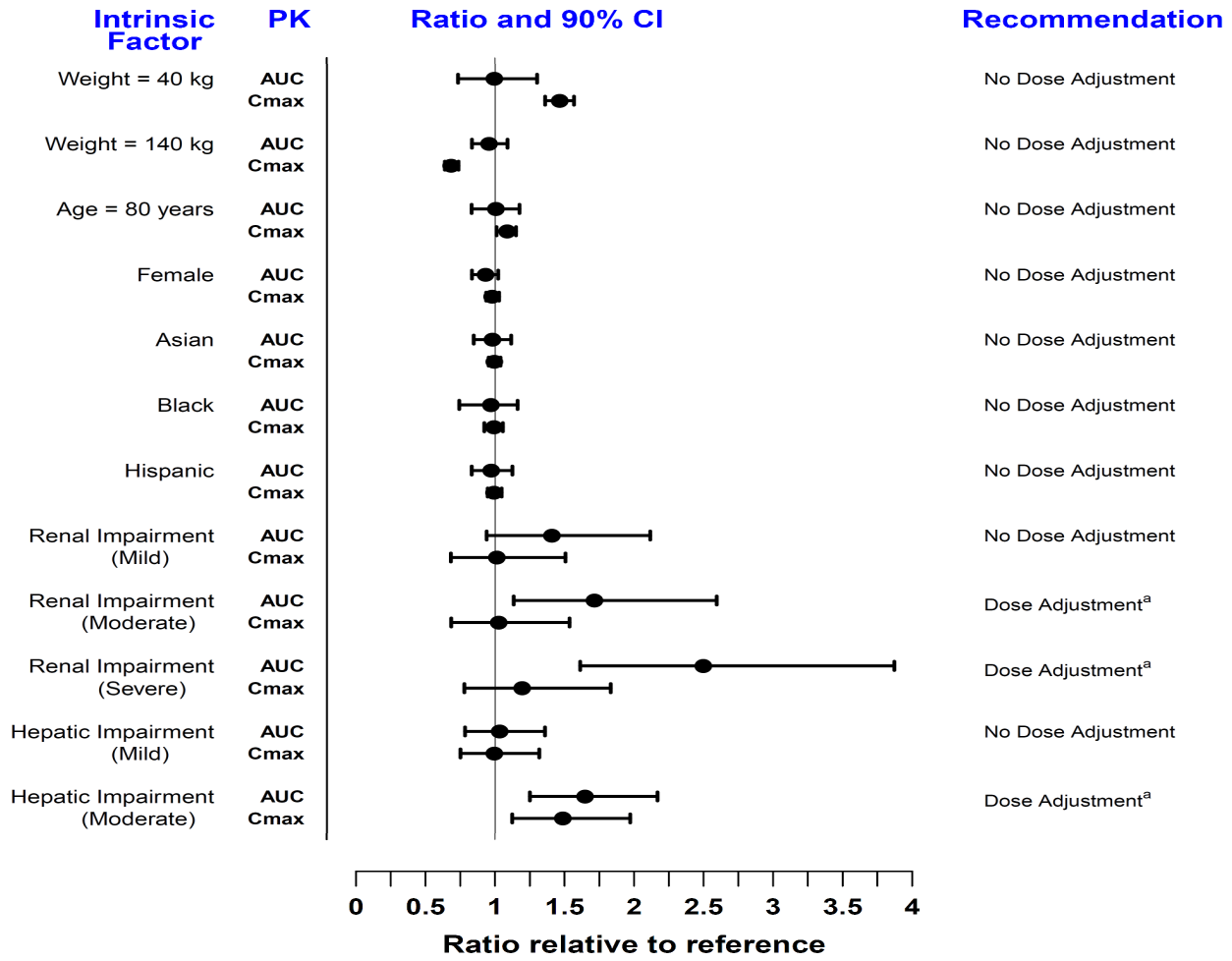
[a.] Pharmacokinetic parameters estimated based on population pharmacokinetic analysis.

Specific Populations

Covariate evaluation as part of population PK analyses in patient populations 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 less than 5% higher AUC relative to the mean age of 55 years for RA patients. 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 approximately linear relationship between body weight and volume of distribution was observed, resulting in higher peak (C_{max}) and lower trough (C_{min}) concentrations in lighter patients. However, this difference is not considered to be clinically relevant.

The effect of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics of tofacitinib is shown in Figure 4.

Figure 4: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics



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

[a] (see section 4.2) for dosage adjustment in RA, PsA, AS and UC patients.

In subjects with ESRD maintained on hemodialysis, mean AUC was approximately 40% higher compared with historical healthy subject data, consistent with approximately 30% contribution of renal clearance to the total clearance of tofacitinib. Dose adjustment is recommended in ESRD patients maintained on hemodialysis (see section 4.2) for dosage adjustment in RA, PsA, AS and UC patients).

Drug Interaction Studies

Potential for Tofacitinib 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 C_{max} of a 5 mg twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the pharmacokinetics of midazolam, a highly sensitive CYP3A4 substrate, when co-administered with tofacitinib.

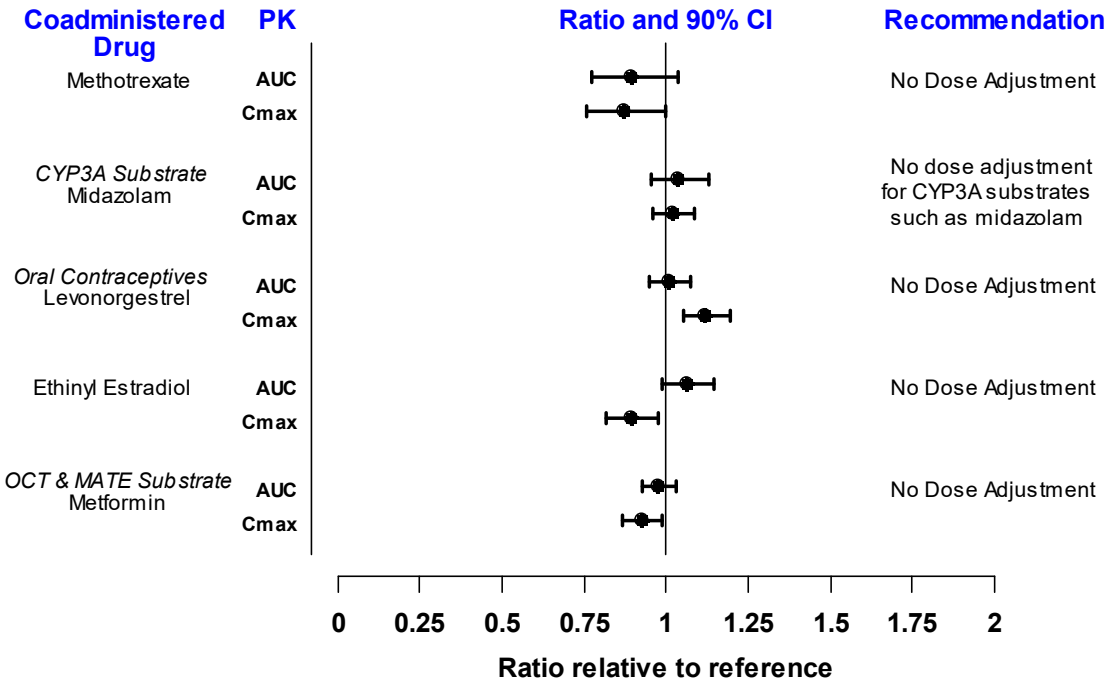
In vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug-metabolizing uridine 5'-diphospho-glucuronosyltransferases (UGTs) [UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7] at concentrations exceeding 250 times the steady state C_{max} of a 5 mg twice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

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

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

Dosing recommendations for coadministered drugs following administration with tofacitinib are shown in Figure 5.

Figure 5. Impact of Tofacitinib on the Pharmacokinetics of Other Drugs

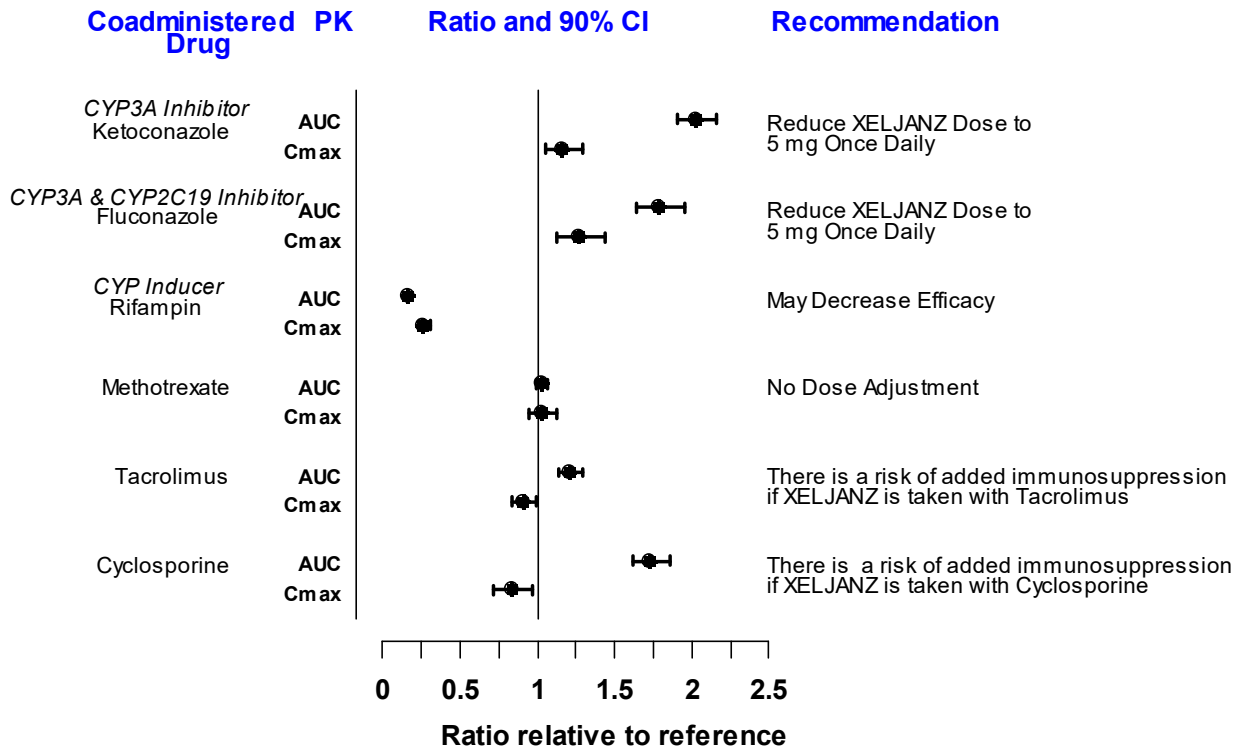


Note: Reference group is administration of concomitant medication alone; OCT = Organic Cationic Transporter; MATE = Multidrug and Toxic Compound Extrusion

Potential for Other Drugs to Influence the Pharmacokinetics of Tofacitinib

Since tofacitinib is metabolized by CYP3A4, interaction with drugs that inhibit or induce CYP3A4 is likely. Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to substantially alter the pharmacokinetics of tofacitinib (see Figure 6).

Figure 6. Impact of Other Drugs on PK of Tofacitinib



Note: Reference group is administration of tofacitinib alone
[a] (See sections 4.2 and 4.4)

6 NONCLINICAL PROPERTIES

6.1 Animal toxicology or pharmacology

Carcinogenesis, Mutagenesis and Impairment of Fertility
In a 39-week toxicology study in monkeys, tofacitinib at exposure levels approximately 6 times the recommended dose of 5 mg twice daily (on an AUC basis at oral doses of 5 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1 times the human dose (on an AUC basis at oral doses of 1 mg/kg twice daily).

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib, at exposure levels approximately 34 times the recommended dose of 5 mg twice daily (on an AUC basis at oral doses of 200 mg/kg/day) was not carcinogenic in mice.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hibernomas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 30 mg/kg/day (approximately 42 times the exposure levels at the human dose on an AUC basis). The relevance of benign Leydig cell tumors to human risk is not known.

Tofacitinib was not mutagenic in the bacterial reverse mutation assay. It was positive for clastogenicity in the *in vitro* chromosome aberration assay with human lymphocytes in the presence of metabolic enzymes, but negative in the absence of metabolic enzymes. Tofacitinib was negative in the *in vivo* rat micronucleus assay and in the *in vitro* CHO-HGPRT assay and the *in vivo* rat hepatocyte unscheduled DNA synthesis assay.

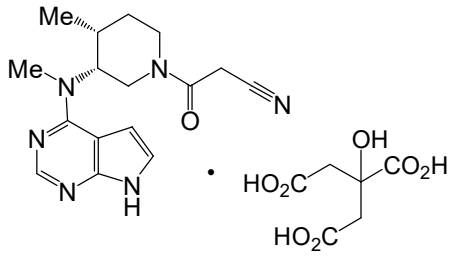
In rats, tofacitinib at exposure levels approximately 17 times the recommended dose of 5 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the recommended dose of 5 mg twice daily (on an AUC basis at oral doses of 1 mg/kg/day). Tofacitinib exposure levels at approximately 133 times the recommended dose of 5 mg twice daily (on an AUC basis at oral doses of 100 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration.

7. DESCRIPTION

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

The solubility of tofacitinib citrate in water is 2.9 mg/mL.

Tofacitinib citrate has a molecular weight of 504.5 Daltons (or 312.4 Daltons as the tofacitinib free base) and a molecular formula of $C_{16}H_{20}N_6O \bullet C_6H_8O_7$. The chemical structure of tofacitinib citrate is:



XELJANZ® is supplied for oral administration as a 5 mg white round, immediate-release film-coated tablet.

Each tablet of XELJANZ® contains 5 mg tofacitinib (equivalent to 8.08 mg tofacitinib citrate) and the following inactive ingredients: croscarmellose sodium, HPMC 2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

36 Months

8.3 Packaging information

HDPE bottles (high-density polyethylene bottles) with desiccant and closures with induction seal liners containing 60 film-coated tablets.

1 Foil/foil blisters containing 14 film-coated tablets per pack.
2 Foil/foil blisters containing 14 film-coated tablets each per pack.

Not all pack sizes may be marketed.

8.4 Storage and handling instructions

Recommended storage condition: Store below 30°C.

No specific handling requirements.

9. PATIENT COUNSELING INFORMATION

Serious Infections
Inform patients that tofacitinib may lower the ability of their immune system to fight infections. Advise patients not to start taking tofacitinib if they have an active infection. Instruct patients to contact their healthcare provider immediately during treatment if symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment (see section 4.4).

Advise patients that the risk of herpes zoster, some cases of which can be serious, is increased in patients treated with tofacitinib (see section 4.4).

Malignancies and Lymphoproliferative Disorders
Inform patients that tofacitinib may increase their risk of certain cancers, and that lymphoma and other cancers have been observed in patients taking tofacitinib. Instruct patients to inform their healthcare provider if they have ever had any type of cancer (see section 4.4).

Major Adverse Cardiovascular Events
Inform patients that Tofacitinib may increase their risk of major adverse cardiovascular events (MACE) defined as myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events (see section 4.4.).

Thrombosis
Advise patients to stop taking tofacitinib and to call their healthcare provider right away if they experience any symptoms of thrombosis (sudden shortness of breath, chest pain worsened with breathing, swelling of leg or arm, leg pain or tenderness, red or discolored skin in the affected leg or arm) (see section 4.4).

Hypersensitivity
Advise patients to stop taking tofacitinib and to call their healthcare provider right away if they experience any symptoms of allergic reactions while taking tofacitinib (see section 4.4).

Important Information on Laboratory Abnormalities
Inform patients that tofacitinib may affect certain lab test results, and that blood tests are required before and during tofacitinib treatment (see section 4.4).

Pregnancy
Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy.

Lactation
Advise women not to breastfeed during treatment with tofacitinib and for at least 18 hours after the last dose of tofacitinib (see section 4.6).

Infertility
Advise females of reproductive potential that tofacitinib may impair fertility (see sections 4.6 and 6.1). It is not known if this effect is reversible.

10. DETAILS OF MANUFACTURER

Manufactured by:
M/s. Pfizer Manufacturing Deutschland GmbH Betriebsstätte Freiburg Mooswaldallee 1, 79090 Freiburg, Germany

Imported & Marketed by: Pfizer Limited, The Capital- A Wing, 1802, 18th Floor, Plot No. C-70, G Block, Bandra - Kurla Complex, Bandra (East), Mumbai 400 051, India

11. DETAILS OF PERMISSION OR LICENSE NUMBER WITH DATE

Import & Marketing Permission No. IMP/ND/47/2016 dt 1st April 2016, IMP/SND/20/000060 dt 4th August 2020, IMP/SND/21/000091 dt 13th September 2021 and IMP/SND/22/000072 dt 17 Oct 2022.

12. DATE OF REVISION

This package insert was last revised in February 2023.