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## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. Name of the medicinal product**

Tofacitinib 5mg film coated Tablets

JITRIT

### **2. Qualitative and quantitative composition**

Each tablet contains:

8 mg of Tofacitinib citrate equivalent to 5 mg of Tofacitinib

Excipient with known effect

Each film-coated tablet contains 20 mg of lactose

For the full list of excipients, see section 6.1.

### **3. Pharmaceutical form**

Film-coated Tablet

White to off-white, circular shaped, biconvex film coated tablets debossed with 'TC' on one face and '5' on other face.

### **4. Clinical particulars**

#### **4.1 Therapeutic indications**

##### Rheumatoid arthritis

Tofacitinib in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

##### Psoriatic arthritis



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

#### Ankylosing spondylitis

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

#### Ulcerative colitis

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

#### Juvenile idiopathic arthritis (JIA)

Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs.

Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

### **4.2 Posology and method of administration**

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which tofacitinib is indicated.

#### Posology

##### *Rheumatoid arthritis and psoriatic arthritis*

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



No dose adjustment is required when used in combination with MTX.

For information on switching between tofacitinib film-coated tablets and tofacitinib prolonged-release tablets see Table 1.

**Table 1: Switching between tofacitinib film-coated tablets and tofacitinib prolonged-release tablets**

Switching between tofacitinib 5 mg film-coated tablets and tofacitinib 11 mg prolonged-release tablet <sup>a</sup>	Treatment with tofacitinib 5 mg film-coated tablets twice daily and tofacitinib 11 mg prolonged-release tablet once daily may be switched between each other on the day following the last dose of either tablet.
<sup>a</sup> See section Pharmacokinetic properties for comparison of pharmacokinetics of prolonged-release and film-coated formulations.	

### Ankylosing spondylitis

The recommended dose of tofacitinib is 5 mg administered twice daily.

### Ulcerative colitis

#### *Induction treatment*

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

For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. Tofacitinib induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

#### *Maintenance treatment*

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

Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known venous thromboembolism (VTE) risk factors, unless there is no suitable alternative treatment available.



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

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

#### *Retreatment in UC*

If therapy is interrupted, restarting treatment with tofacitinib can be considered. If there has been a loss of response, reinduction with tofacitinib 10 mg twice daily may be considered. The treatment interruption period in clinical studies extended up to 1 year. Efficacy may be regained by 8 weeks of 10 mg twice daily therapy.

#### *Polyarticular JIA and juvenile PsA (children between 2 and 18 years of age)*

Tofacitinib may be used as monotherapy or in combination with MTX.

The recommended dose in patients 2 years of age and older is based upon the following weight categories:

**Table 2: Tofacitinib dose for patients with polyarticular juvenile idiopathic arthritis and juvenile PsA two years of age and older**

Body weight (kg)	Dose regimen
10 - < 20	3.2 mg (3.2 mL of oral solution) twice daily
20 - < 40	4 mg (4 mL of oral solution) twice daily
≥ 40	5 mg (5 mL of oral solution or 5 mg film-coated tablet) twice daily

Patients ≥ 40 kg treated with tofacitinib 5 mL oral solution twice daily may be switched to tofacitinib 5 mg film-coated tablets twice daily. Patients < 40 kg cannot be switched from tofacitinib oral solution.



### Dose interruption and discontinuation in adults and paediatric patients

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

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia, and anaemia. As described in Tables 3, 4 and 5 below, recommendations for temporary dose interruption or permanent discontinuation of treatment are made according to the severity of laboratory abnormalities.

It is recommended not to initiate dosing in patients with an absolute lymphocyte count (ALC) less than 750 cells/mm<sup>3</sup>.

**Table 3: Low absolute lymphocyte count**

<b>Low absolute lymphocyte count (ALC)</b>	
<b>Lab value (cells/mm<sup>3</sup>)</b>	<b>Recommendation</b>
ALC greater than or equal to 750	Dose should be maintained.
ALC 500-750	For persistent (2 sequential values in this range on routine testing) decrease in this range, dosing should be reduced or interrupted.  For patients receiving tofacitinib 10 mg twice daily, dosing should be reduced to tofacitinib 5 mg twice daily.  For patients receiving tofacitinib 5 mg twice daily, dosing should be interrupted.  When ALC is greater than 750, treatment should be resumed as clinically appropriate.
ALC less than 500	If lab value confirmed by repeats testing within 7 days, dosing



	should be discontinued.
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It is recommended not to initiate dosing in adult patients with an absolute neutrophil count (ANC) less than 1,000 cells/mm<sup>3</sup>. It is recommended not to initiate dosing in paediatric patients with an absolute neutrophil count (ANC) less than 1,200 cells/mm<sup>3</sup>.

**Table 4: Low absolute neutrophil count**

Low absolute neutrophil count (ANC)	
Lab Value (cells/mm <sup>3</sup> )	Recommendation
ANC greater than 1,000	Dose should be maintained.
ANC 500-1,000	For persistent (2 sequential values in this range on routine testing) decreases in this range, dosing should be reduced or interrupted.  For patients receiving tofacitinib 10 mg twice daily, dosing should be reduced to tofacitinib 5 mg twice daily.  For patients receiving tofacitinib 5 mg twice daily, dosing should be interrupted.  When ANC is greater than 1,000, treatment should be resumed as clinically appropriate.
ANC less than 500	If lab value confirmed by repeats testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in adult patients with haemoglobin less than 9 g/dL. It is recommended not to initiate dosing in paediatric patients with haemoglobin less than 10 g/dL.

**Table 5: Low haemoglobin value**

Low haemoglobin value	
Lab value	Recommendation



(g/dL)	
Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Dose should be maintained.
Greater than 2 g/dL decrease or less than 8.0 g/dL (confirmed by repeat testing)	Dosing should be interrupted until haemoglobin values have normalised.

### Interactions

Tofacitinib total daily dose should be reduced by half in patients receiving potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) and in patients receiving 1 or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g., fluconazole) as follows:

- Tofacitinib dose should be reduced to 5 mg once daily in patients receiving 5 mg twice daily (adult and paediatric patients).
- Tofacitinib dose should be reduced to 5 mg twice daily in patients receiving 10 mg twice daily (adult patients).

Only in paediatric patients: available data suggest that clinical improvement is observed within 18 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

### Dose discontinuation in AS

Available data suggest that clinical improvement in AS is observed within 16 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

### Special populations

#### *Elderly*



No dose adjustment is required in patients aged 65 years and older. There are limited data in patients aged 75 years and older. See section Special warnings and precautions for use for Use in patients over 65 years of age.

#### *Hepatic impairment*

**Table 6: Dose adjustment for hepatic impairment**

<b>Hepatic impairment category</b>	<b>Classification</b>	<b>Dose adjustment in hepatic impairment for different strength tablets</b>
Mild	Child Pugh A	No dose adjustment required.
Moderate	Child Pugh B	Dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily.  Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily
Severe	Child Pugh C	Tofacitinib should not be used in patients with severe hepatic impairment

#### *Renal impairment*

**Table 7: Dose adjustment for renal impairment**

<b>Renal impairment category</b>	<b>Creatinine clearance</b>	<b>Dose adjustment in renal impairment for different strength tablets</b>
Mild	50-80 mL/min	No dose adjustment required.
Moderate	30-49 mL/min	No dose adjustment required.
Severe (including patients undergoing	< 30 mL/min	Dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal renal



haemodialysis)		<p>function is 5 mg twice daily.</p> <p>Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily.</p> <p>Patients with severe renal impairment should remain on a reduced dose even after haemodialysis</p>
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#### *Paediatric population*

The safety and efficacy of tofacitinib in children less than 2 years of age with polyarticular JIA and juvenile PsA has not been established. No data are available.

The safety and efficacy of tofacitinib in children less than 18 years of age with other indications (e.g., ulcerative colitis) has not been established. No data are available.

#### Method of administration

Oral use.

Tofacitinib is given orally with or without food.

For patients who have difficulties swallowing, tofacitinib tablets may be crushed and taken with water.

#### **4.3 Contraindications**

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active tuberculosis (TB), serious infections such as sepsis, or opportunistic infections
- Severe hepatic impairment
- Pregnancy and lactation

#### **4.4 Special warning and precautions for use**

Use in patients over 65 years of age



Considering the increased risk of serious infections, myocardial infarction, and malignancies with tofacitinib in patients over 65 years of age, tofacitinib should only be used in these patients if no suitable treatment alternatives are available.

Combination with other therapies

Tofacitinib has not been studied and its use should be avoided in combination with biologics such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, selective co-stimulation modulators and potent immunosuppressant's such as azathioprine, 6-mercaptopurine, ciclosporine and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

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

The use of tofacitinib in combination with phosphodiesterase 4 inhibitors has not been studied in tofacitinib clinical studies.

Venous thromboembolism (VTE)

Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), have been observed in patients taking tofacitinib. A dose dependent increased risk for VTE was observed in a clinical study with tofacitinib compared to TNF inhibitors.

In a post hoc exploratory analysis within this study, in patients with known VTE risk factors, occurrences of subsequent VTEs were observed more frequently in tofacitinib-treated patients that, at 12 months treatment, had D-dimer level  $\geq 2 \times$  ULN versus those with D-dimer level  $< 2 \times$  ULN; this was not evident in TNF inhibitor-treated patients. Interpretation is limited by the low number of VTE events and restricted D-dimer test availability (only assessed at Baseline, Month 12, and at the end of the study). In patients who did not have a VTE during the study, mean D-dimer levels were significantly reduced at Month 12 relative to Baseline across all treatment



arms. However, D-dimer levels  $\geq 2 \times$  ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D-Dimer testing in this study.

Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage.

Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available. VTE risk factors include previous VTE, patients undergoing major surgery, immobilization, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (BMI  $\geq 30$ ), diabetes, hypertension, smoking status should also be considered. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.

Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.

### 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 risk of opportunistic infections is higher in Asian geographic regions. Rheumatoid arthritis patients taking corticosteroids may be predisposed to infection.

Tofacitinib should not be initiated in patients with active infections, including localised infections.

The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients:

- with recurrent infections,
- with a history of a serious or an opportunistic infection,
- who have resided or travelled in areas of endemic mycoses,
- who have underlying conditions that may predispose them to infection.



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

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients over 65 years of age tofacitinib should only be used if no suitable treatment alternatives are available.

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

### Tuberculosis

The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients:

- who have been exposed to TB,
- who have resided or travelled in areas of endemic TB.

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

Patients with latent TB, who test positive, should be treated with standard antimycobacterial therapy before administering tofacitinib.

Antituberculosis therapy should also be considered prior to administration of tofacitinib in patients who test negative for TB but who have a past history of latent or active TB and where an adequate course of treatment cannot be confirmed; or those who test negative but who have risk factors for TB infection. Consultation with a healthcare professional with expertise in the treatment of TB is recommended to aid in the decision about whether initiating antituberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the



development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

#### Viral reactivation

Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with tofacitinib. In patients treated with tofacitinib, the incidence of herpes zoster appears to be increased in:

- Japanese or Korean patients.
- Patients with an ALC less than 1,000 cells/mm<sup>3</sup>.
- Patients with long standing RA who have previously received two or more biological disease modifying antirheumatic drugs (DMARDs).
- Patients treated with 10 mg twice daily.

The impact of tofacitinib on chronic viral hepatitis reactivation is unknown. Patients 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.

#### Major adverse cardiovascular events (including myocardial infarction)

Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib. In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared to TNF inhibitors. In patients over 65 years of age, patients who are current or past smokers, and patients with other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.

#### Malignancy and lymph proliferative disorder

Tofacitinib may affect host defenses against malignancies.

In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of

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malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors.

Lung cancers and lymphoma in patients treated with tofacitinib have also been observed in other clinical studies and in the post marketing setting.

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

In patients over 65 years of age, patients who are current or past smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.

Non-melanoma skin cancer

NMSCs have been reported in patients treated with tofacitinib. The risk of NMSC may be higher in patients treated with tofacitinib 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Interstitial lung disease

Caution is also recommended in patients with a history of chronic lung disease as they may be more prone to infections. Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with tofacitinib in RA clinical trials and in the post-marketing setting although the role of Janus kinase (JAK) inhibition in these events is not known. Asian RA patients are known to be at higher risk of interstitial lung disease, thus caution should be exercised in treating these patients.

Gastrointestinal perforations

Events of gastrointestinal perforation have been reported in clinical trials although the role of JAK inhibition in these events is not known. Tofacitinib should be used with caution in patients

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who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis, patients with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory drugs). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Liver enzymes

Treatment with tofacitinib was associated with an increased incidence of liver enzyme elevation in some patients (see section Undesirable effects liver enzyme tests). Caution should be exercised when considering initiation of tofacitinib treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST), particularly when initiated in combination with potentially hepatotoxic medicinal products such as MTX. Following initiation, routine monitoring of liver tests and prompt investigation of the causes of any observed liver enzyme elevations are 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.

Hypersensitivity

In post-marketing experience, cases of drug hypersensitivity associated with tofacitinib administration have been reported. Allergic reactions included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, tofacitinib should be discontinued immediately.

Laboratory parameters

*Lymphocytes*

Treatment with tofacitinib was associated with an increased incidence of lymphopenia compared to placebo. Lymphocyte counts less than 750 cells/mm<sup>3</sup> were associated with an increased incidence of serious infections. It is not recommended to initiate or continue tofacitinib treatment in patients with a confirmed lymphocyte count less than 750 cells/mm<sup>3</sup>. Lymphocytes should be



monitored at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts, see section dosage and administration.

#### Neutrophils

Treatment with tofacitinib was associated with an increased incidence of neutropenia (less than 2,000 cells/mm<sup>3</sup>) compared to placebo. It is not recommended to initiate tofacitinib treatment in adult patients with an ANC less than 1,000 cells/mm<sup>3</sup> and in paediatric patients with an ANC less than 1,200 cells/mm<sup>3</sup>. ANC should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on ANC, see section dosage and administration.

#### Haemoglobin

Treatment with tofacitinib has been associated with decreases in haemoglobin levels. It is not recommended to initiate tofacitinib treatment in adult patients with a haemoglobin value less than 9 g/dL and in paediatric patients with a haemoglobin value less than 10 g/dL. Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on haemoglobin level, see section dosage and administration.

#### Lipid monitoring

Treatment with tofacitinib was associated with increases in lipid parameters such as total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. Assessment of lipid parameters should be performed after 8 weeks following initiation of tofacitinib therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidemia. Increases in total and LDL cholesterol associated with tofacitinib may be decreased to pretreatment levels with statin therapy.

#### Vaccinations



Prior to initiating tofacitinib, it is recommended that all patients, particularly pJIA and jPsA patients, be brought up to date with all immunizations in agreement with current immunization guidelines. It is recommended that live vaccines not be given concurrently with tofacitinib. The decision to use live vaccines prior to tofacitinib treatment should take into account the pre-existing immunosuppression in a given patient.

Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular consideration should be given to patients with longstanding RA who have previously received two or more biological DMARDs. If live zoster vaccine is administered; it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus (VZV). If the history of chickenpox is considered doubtful or unreliable it is recommended to test for antibodies against VZV.

Vaccination with live vaccines should occur at least 2 weeks but preferably 4 weeks prior to initiation of tofacitinib or in accordance with current vaccination guidelines regarding immunomodulatory medicinal products. No data are available on the secondary transmission of infection by live vaccines to patients receiving tofacitinib.

#### Excipients contents

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

#### **4.5 Interactions with Other Medicaments**

Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib  
Since tofacitinib is metabolised by CYP3A4, interaction with medicinal products that inhibit or induce CYP3A4 is likely. Tofacitinib exposure is increased when coadministered with potent inhibitors of CYP3A4 (e.g., ketoconazole) or when administration of one or more concomitant



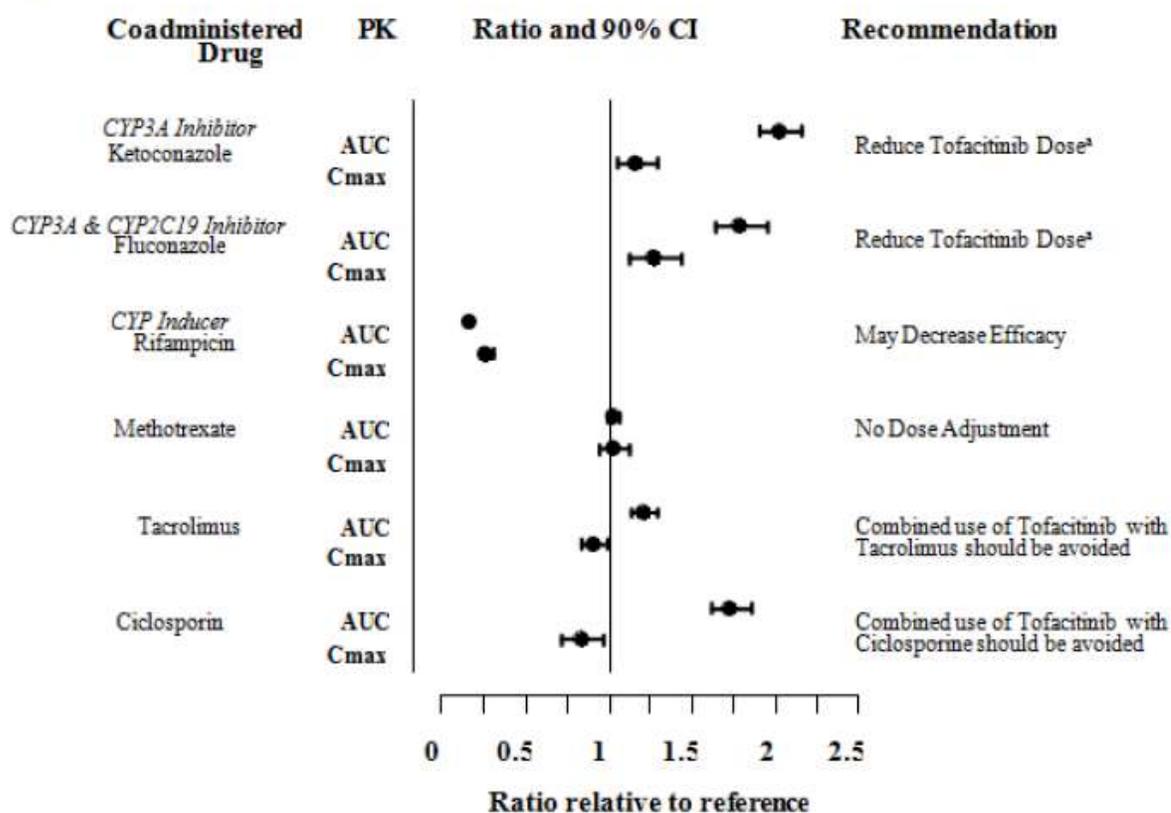
medicinal products results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

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

Coadministration with ketoconazole (strong CYP3A4 inhibitor), fluconazole (moderate CYP3A4 and potent CYP2C19 inhibitor), tacrolimus (mild CYP3A4 inhibitor) and ciclosporine (moderate CYP3A4 inhibitor) increased tofacitinib AUC, while rifampicin (potent CYP inducer) decreased tofacitinib AUC. Coadministration of tofacitinib with potent CYP inducers (e.g., rifampicin) may result in a loss of or reduced clinical response. Coadministration of potent inducers of CYP3A4 with tofacitinib is not recommended. Coadministration with ketoconazole and fluconazole increased tofacitinib  $C_{max}$ , while tacrolimus, ciclosporine and rifampicin decreased tofacitinib  $C_{max}$ . Concomitant administration with MTX 15-25 mg once weekly had no effect on the PK of tofacitinib in RA patients



Figure 1. Impact of Other Medicinal Products on PK of Tofacitinib



Note: Reference group is administration of tofacitinib alone.

<sup>a</sup> Tofacitinib dose should be reduced to 5 mg twice daily in patients receiving 10 mg twice daily. Tofacitinib dose should be reduced to 5 mg once daily in patients receiving 5 mg twice daily

*Potential for tofacitinib to influence the PK of other medicinal products*

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

In RA patients, coadministration of tofacitinib with MTX 15-25 mg once weekly decreased the AUC and C<sub>max</sub> of MTX by 10% and 13%, respectively. The extent of decrease in MTX exposure does not warrant modifications to the individualized dosing of MTX.



#### **4.6 Fertility, pregnancy and lactation**

##### ***Pregnancy***

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

As a precautionary measure, the use of tofacitinib during pregnancy is contraindicated

##### ***Women of childbearing potential/contraception in females***

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

##### ***Breast-feeding***

It is not known whether tofacitinib is secreted in human milk. A risk to the breast-fed child cannot be excluded. Tofacitinib was secreted in the milk of lactating rats. As a precautionary measure, the use of tofacitinib during breast-feeding is contraindicated

##### ***Fertility***

Formal studies of the potential effect on human fertility have not been conducted. Tofacitinib impaired female fertility but not male fertility in rats.

#### **4.7 Effects on ability to drive and use machine**

Tofacitinib has no or negligible influence on the ability to drive and use machines.

#### **4.8 Undesirable effects**

Summary of the safety profile

##### ***Rheumatoid arthritis***

The most common serious adverse reactions were serious infections. The most common serious infections reported with tofacitinib were pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, TB and other



mycobacterial infections, Cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus, BK virus infections and listeriosis were reported with tofacitinib. Some patients have presented with disseminated rather than localised disease. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials were headache, upper respiratory tract infections, nasopharyngitis, diarrhoea, nausea and hypertension. (see Table 6, Adverse Drug Reactions [ADRs] based on all study durations)

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

#### *Psoriatic arthritis*

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

#### *Ankylosing spondylitis*

Overall, the safety profile observed in patients with active AS treated with tofacitinib was consistent with the safety profile observed in patients with RA treated with tofacitinib.

#### *Ulcerative colitis*

The most commonly reported adverse reactions in patients receiving tofacitinib 10 mg twice daily in the induction studies were headache, nasopharyngitis, nausea, and arthralgia.

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



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

### *Tabulated list of adverse reactions*

The ADRs listed in the table below are from clinical studies in patients with RA, PsA, and UC and are presented by System Organ Class (SOC) and frequency categories, defined using the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 6: Adverse Drug Reactions**

System Organ Class	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$	Rare $\geq 1/10,000$ to $< 1/1,000$	Very Rare $< 1/10,000$	Not Known (cannot be estimated from the available data)
Infections and infestations	Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Nasopharyngitis Pharyngitis	Tuberculosis Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection	Sepsis Urosepsis Disseminated TB Necrotizing fasciitis Bacteraemia Staphylococcal bacteraemia <i>Pneumocystis jirovecii</i> pneumonia Pneumonia pneumococcal	Tuberculosis of central nervous system Meningitis cryptococcal <i>Mycobacterium avium</i> complex infection	



			Pneumonia bacterial Encephalitis Atypical mycobacterial infection Cytomegalovirus infection Arthritis bacterial		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Non-melanoma skin cancers			
Blood and lymphatic system disorders	Anaemia	Leukopenia Lymphopenia Neutropenia			
Immune system disorders					Drug hypersensitivity* Angioedema* Urticaria*
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia Dehydration			
Psychiatric		Insomnia			



disorders					
Nervous system disorders	Headache	Paraesthesia			
Vascular disorders	Hypertension				
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea Sinus congestion			
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia				
Hepatobiliary disorders		Hepatic steatosis			
Skin and subcutaneous tissue disorders	Rash	Erythema Pruritus			
Musculoskeletal and connective tissue disorders	Arthralgia	Musculoskeletal pain Joint swelling Tendonitis			
General disorders and administration	Pyrexia Oedema peripheral				



site conditions	Fatigue				
Investigations	Blood creatine phosphokinase increased	Hepatic enzyme increased Transaminases increased Liver function test abnormal Gamma glutamyl-transferase increased Blood creatinine increased Blood cholesterol increased Low density lipoprotein increased Weight increased			
Injury, poisoning and procedural complications		Ligament sprain Muscle strain			

\*Spontaneous reporting data

\*\*Venous thromboembolism includes PE and DVT



Description of selected adverse reactions

*Venous thromboembolism*

*Rheumatoid arthritis*

In a large, randomised post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors. The majority of these events were serious and some resulted in death. The incidence rates (95% CI) for PE for tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, and TNF inhibitors were 0.54 (0.32-0.87), 0.27 (0.12-0.52), and 0.09 (0.02-0.26) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for PE was 5.96 (1.75-20.33) and 2.99 (0.81-11.06) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily, respectively (see section 5.1).

In a subgroup analysis in patients with VTE risk factors in the above-mentioned study, the risk for PE was further increased. Compared with TNF inhibitors, the HR for PE was 9.14 (2.11-39.56) for tofacitinib 10 mg twice daily and 3.92 (0.83-18.48) for tofacitinib 5 mg twice daily.

*Ankylosing spondylitis*

In the combined Phase 2 and Phase 3 randomised controlled clinical studies, there were no VTE events in 420 patients (233 patient-years of observation) receiving tofacitinib up to 48 weeks.

*Ulcerative colitis (UC)*

In the UC on-going extension trial, cases of PE and DVT have been observed in patients using tofacitinib 10 mg twice daily and with underlying VTE risk factor(s).

*Overall infections*

*Rheumatoid arthritis*

In controlled Phase 3 clinical studies, the rates of infections over 0-3 months in the 5 mg twice daily (total 616 patients) and 10 mg twice daily (total 642 patients) tofacitinib monotherapy groups were 16.2% (100 patients) and 17.9% (115 patients), respectively, compared to 18.9%



(23 patients) in the placebo group (total 122 patients). In controlled Phase 3 clinical studies with background DMARDs, the rates of infections over 0-3 months in the 5 mg twice daily (total 973 patients) and 10 mg twice daily (total 969 patients) tofacitinib plus DMARD group were 21.3% (207 patients) and 21.8% (211 patients), respectively, compared to 18.4% (103 patients) in the placebo plus DMARD group (total 559 patients).

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

The overall incidence rate of infections with tofacitinib in the long-term safety all exposure population (total 4,867 patients) was 46.1 patients with events per 100 patient-years (43.8 and 47.2 patients with events for 5 mg and 10 mg twice daily, respectively). For patients (total 1,750) on monotherapy, the rates were 48.9 and 41.9 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively. For patients (total 3,117) on background DMARDs, the rates were 41.0 and 50.3 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively.

#### *Ankylosing spondylitis*

In the combined Phase 2 and Phase 3 clinical studies, during the placebo-controlled period of up to 16 weeks, the frequency of infections in the tofacitinib 5 mg twice daily group (185 patients) was 27.6% and the frequency in the placebo group (187 patients) was 23.0%. In the combined Phase 2 and Phase 3 clinical studies, among the 316 patients treated with tofacitinib 5 mg twice daily for up to 48 weeks, the frequency of infections was 35.1%.

#### *Ulcerative colitis*

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

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**TOFACITINIB TABLET 5 mg (JITRIT)**

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

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

*Serious infections*

*Rheumatoid arthritis*

In the 6-month and 24-month, controlled clinical studies, the rate of serious infections in the 5 mg twice daily tofacitinib monotherapy group was 1.7 patients with events per 100 patient-years. In the 10 mg twice daily tofacitinib monotherapy group the rate was 1.6 patients with events per 100 patient-years, the rate was 0 events per 100 patient-years for the placebo group, and the rate was 1.9 patients with events per 100 patient-years for the MTX group.

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

In the long-term safety all exposure population, the overall rates of serious infections were 2.4 and 3.0 patients with events per 100 patient-years for 5 mg and 10 mg twice daily tofacitinib groups, respectively. The most common serious infections included pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis and diverticulitis. Cases of opportunistic infections have been reported.

*Ulcerative colitis*

The incidence rates and types of serious infections in the UC clinical studies were generally similar to those reported in RA clinical studies with tofacitinib monotherapy treatment groups.



*Ankylosing spondylitis*

In the combined Phase 2 and Phase 3 clinical studies, among the 316 patients treated with tofacitinib 5 mg twice daily for up to 48 weeks, there was one serious infection (aseptic meningitis) yielding a rate of 0.43 patients with events per 100 patient-years.

*Serious infections in the elderly*

Of the 4,271 patients who enrolled in RA studies I-VI, a total of 608 RA patients were 65 years of age and older, including 85 patients 75 years and older. The frequency of serious infection among tofacitinib-treated patients 65 years of age and older was higher than those under the age of 65 (4.8 per 100 patient-years versus 2.4 per 100 patient-years, respectively). As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

*Serious infections from non-interventional post approval safety study*

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



*Viral reactivation*

Patients treated with tofacitinib who are Japanese or Korean, or patients with long standing RA who have previously received two or more biological DMARDs, or patients with an ALC less than 1,000 cells/mm<sup>3</sup>, or patients treated with 10 mg twice daily may have an increased risk of herpes zoster.

***Laboratory tests***

*Lymphocytes*

In the controlled RA clinical studies, confirmed decreases in ALC below 500 cells/mm<sup>3</sup> occurred in 0.3% of patients and for ALC between 500 and 750 cells/mm<sup>3</sup> in 1.9% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

In the RA long-term safety population, confirmed decreases in ALC below 500 cells/mm<sup>3</sup> occurred in 1.3% of patients and for ALC between 500 and 750 cells/mm<sup>3</sup> in 8.4% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

Confirmed ALC less than 750 cells/mm<sup>3</sup> were associated with an increased incidence of serious infections.

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

*Neutrophils*

In the controlled RA clinical studies, confirmed decreases in ANC below 1,000 cells/mm<sup>3</sup> occurred in 0.08% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. There were no confirmed decreases in ANC below 500 cells/mm<sup>3</sup> observed in any treatment group. There was no clear relationship between neutropenia and the occurrence of serious infections.

In the RA long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical studies.



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

*Liver enzyme tests*

Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were uncommonly observed in RA patients. In those 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 normalisation of liver enzymes.

In the controlled portion of the RA Phase 3 monotherapy study (0-3 months), ALT elevations greater than 3x ULN were observed in 1.65%, 0.41%, and 0% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 1.65%, 0.41% and 0% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the RA Phase 3 monotherapy study (0-24 months) (study VI, , ALT elevations greater than 3x ULN were observed in 7.1%, 3.0%, and 3.0% of patients receiving MTX, tofacitinib 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 3.3%, 1.6% and 1.5% of patients receiving MTX, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the controlled portion of the RA Phase 3 studies on background DMARDs (0-3 months) (studies II-V, ), ALT elevations greater than 3x ULN were observed in 0.9%, 1.24% and 1.14% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively. In these studies, AST elevations greater than 3x ULN were observed in 0.72%, 0.5% and 0.31% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the RA long-term extension studies, on monotherapy, ALT elevations greater than 3x ULN were observed in 1.1% and 1.4% of patients receiving tofacitinib 5 mg and 10 mg twice daily, respectively. AST elevations greater than 3x ULN were observed in < 1.0% in both the tofacitinib 5 mg and 10 mg twice daily groups.



In the RA long-term extension studies, on background DMARDs, ALT elevations greater than 3x ULN were observed in 1.8% and 1.6% of patients receiving tofacitinib 5 mg and 10 mg twice daily, respectively. AST elevations greater than 3x ULN were observed in < 1.0% in both the tofacitinib 5 mg and 10 mg twice daily groups.

In the clinical studies in UC, changes in liver enzyme tests observed with tofacitinib treatment were similar to the changes observed in clinical studies in RA.

### *Lipids*

Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were first assessed at 1 month following initiation of tofacitinib in the controlled double-blind clinical trials of RA. Increases were observed at this time point and remained stable thereafter.

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

- Mean LDL cholesterol increased by 15% in the tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at month 12, and increased by 16% in the tofacitinib 5 mg twice daily arm and 19% in the tofacitinib 10 mg twice daily arm at month 24.
- Mean HDL cholesterol increased by 17% in the tofacitinib 5 mg twice daily arm and 18% in the tofacitinib 10 mg twice daily arm at month 12, and increased by 19% in the tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at month 24.

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

Mean LDL cholesterol/HDL cholesterol ratios and Apolipoprotein B (ApoB)/ApoA1 ratios were essentially unchanged in tofacitinib-treated patients.

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



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

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

#### *Myocardial infarction*

##### *Rheumatoid arthritis*

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for non-fatal myocardial infarction for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), and 0.16 (0.07, 0.31) patients with events per 100 patient-years, respectively. Few fatal myocardial infarctions were reported with rates similar in patients treated with tofacitinib compared to TNF. The study required at least 1500 patients to be followed for 3 years.

#### *Malignancies excluding NMSC*

##### *Rheumatoid arthritis*

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for lung cancer for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.23 (0.12, 0.40), 0.32 (0.18, 0.51), and 0.13 (0.05, 0.26) patients with events per 100 patient-years, respectively (see sections Pharmacological properties). The study required at least 1500 patients to be followed for 3 years.

The incidence rates (95% CI) for lymphoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), and 0.02 (0.00, 0.10) patients with events per 100 patient-years, respectively.

#### Paediatric population

##### *Polyarticular juvenile idiopathic arthritis and juvenile PsA*



The adverse reactions in JIA patients in the clinical development program were consistent in type and frequency with those seen in adult RA patients, with the exception of some infections (influenza, pharyngitis, sinusitis, viral infection) and gastrointestinal or general disorders (abdominal pain, nausea, vomiting, pyrexia, headache, cough), which were more common in JIA paediatric population. MTX was the most frequent concomitant csDMARD used (on Day 1, 156 of 157 patients on csDMARDs took MTX). There are insufficient data regarding the safety profile of tofacitinib used concomitantly with any other csDMARDs.

#### Infections

In the double-blind portion of the pivotal Phase 3 trial (Study JIA-I), infection was the most commonly reported adverse reaction (44.3%). The infections were generally mild to moderate in severity.

In the integrated safety population, 7 patients had serious infections during treatment with tofacitinib within the reporting period (up to 28 days after the last dose of study medication), representing an incidence rate of 1.92 patients with events per 100 patient-years: pneumonia, epidural empyema (with sinusitis and subperiosteal abscess), pilonidal cyst, appendicitis, escherichia pyelonephritis, abscess limb, and UTI.

In the integrated safety population, 3 patients had non-serious events of herpes zoster within the reporting window representing an incidence rate of 0.82 patients with events per 100 patient-years. One (1) additional patient had an event of serious HZ outside the reporting window.

#### Hepatic events

Patients in the JIA pivotal study were required to have AST and ALT levels less than 1.5 times the upper limit of normal to be eligible for enrolment. In the integrated safety population, there were 2 patients with ALT elevations  $\geq 3$  times the ULN at 2 consecutive visits. Neither event met Hy's Law criteria. Both patients were on background MTX therapy and each event resolved after discontinuation of MTX and permanent discontinuation of tofacitinib.



#### *Laboratory tests*

Changes in laboratory tests in JIA patients in the clinical development program were consistent with those seen in adult RA patients. Patients in the JIA pivotal study were required to have a platelet count  $\geq 100,000$  cells/mm<sup>3</sup> to be eligible for enrolment, therefore, there is no information available for JIA patients with a platelet count  $<100,000$  cells/mm<sup>3</sup> before starting treatment with tofacitinib.

#### **4.9 Overdose**

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

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

### **5. Pharmacological properties**

#### **5.1 Pharmacodynamic Properties**

Pharmacotherapeutic groups: Immunosuppressants, Selective Immunosuppressants; ATC code: L04AA29

#### *Mechanism of action*

Tofacitinib is a potent, selective inhibitor of the JAK family. In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In contrast, tofacitinib has a high degree of selectivity against other kinases in the human genome. In human cells, tofacitinib preferentially inhibits signalling by heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib attenuates signalling of interleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which will result in modulation of the immune and inflammatory response.

***Pharmacodynamic effects***

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

Following long-term treatment (median duration of tofacitinib treatment of approximately 5 years), CD4+ and CD8+ counts showed median reductions of 28% and 27%, respectively, from baseline. In contrast to the observed decrease after short-term dosing, CD16/56+ natural killer cell counts showed a median increase of 73% from baseline. CD19+ B cell counts showed no further increases after long-term tofacitinib treatment. All these lymphocyte subset changes returned toward baseline after temporary discontinuation of treatment. There was no evidence of a relationship between serious or opportunistic infections or herpes zoster and lymphocyte subset counts.

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

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

**Vaccine studies**

In a controlled clinical trial of patients with RA initiating tofacitinib 10 mg twice daily or placebo, the number of responders to influenza vaccine was similar in both groups: tofacitinib (57%) and placebo (62%). For pneumococcal polysaccharide vaccine the number of responders was as follows: 32% in patients receiving both tofacitinib and MTX; 62% for tofacitinib



monotherapy; 62% for MTX monotherapy; and 77% for placebo. The clinical significance of this is unknown, however, similar results were obtained in a separate vaccine study with influenza and pneumococcal polysaccharide vaccines in patients receiving long-term tofacitinib 10 mg twice daily.

A controlled study was conducted in patients with RA on background MTX immunised with a live attenuated herpes virus vaccine 2 to 3 weeks before initiating a 12-week treatment with tofacitinib 5 mg twice daily or placebo. Evidence of humoral and cell-mediated responses to VZV was observed in both tofacitinib and placebo-treated patients at 6 weeks. These responses were similar to those observed in healthy volunteers aged 50 years and older. A patient with no previous history of varicella infection and no anti-varicella antibodies at baseline experienced dissemination of the vaccine strain of varicella 16 days after vaccination. Tofacitinib was discontinued and the patient recovered after treatment with standard doses of antiviral medication. This patient subsequently made a robust, though delayed, humoral and cellular response to the vaccine.

### Clinical efficacy and safety

#### *Rheumatoid arthritis*

The efficacy and safety of tofacitinib film-coated tablets were assessed in 6 randomised, double-blind, controlled multicentre studies in patients greater than 18 years of age with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Table 9 provides information regarding the pertinent study design and population characteristics.

**Table 9: Phase 3 clinical trials of tofacitinib 5 mg and 10 mg twice daily doses in patients with RA**

Studies	Study I (ORAL Solo)	Study II (ORAL Sync)	Study III (ORAL Standard)	Study IV (ORAL Scan)	Study V (ORAL Step)	Study VI (ORAL Start)	Study VII (ORAL Strategy)
Population	DMARD-IR	DMARD-	MTX-IR	MTX-IR	TNFi-IR	MTX-naïve <sup>a</sup>	MTX-IR



		IR					
Control	Placebo	Placebo	Placebo	Placebo	Placebo	MTX	MTX, ADA
Background treatment	None <sup>b</sup>	csDMARDs	MTX	MTX	MTX	None <sup>b</sup>	3 Parallel arms: <ul style="list-style-type: none"> <li>• Tofacitinib monotherapy</li> <li>• Tofacitinib+MTX</li> <li>• ADA+MTX</li> </ul>
Key features	Monotherapy	Various csDMARDs	Active control (ADA)	X-Ray	TNFi-IR	Monotherapy, Active comparator (MTX), X-Ray	Tofacitinib with and without MTX in comparison to ADA with MTX
Number of patients treated	610	792	717	797	399	956	1,146
Total study duration	6 months	1 year	1 year	2 years	6 months	2 years	1 year
Co-primary efficacy endpoints <sup>c</sup>	Month 3: ACR20 HAQ-DI DAS28-4(ESR)<2.6	Month 6: ACR20 DAS28-4(ESR)<2.6 Month 3: HAQ-DI	Month 6: ACR20 DAS28-4(ESR)<2.6 Month 3: HAQ-DI	Month 6: ACR20 mTSS DAS28-4(ESR)<2.6 Month 3: HAQ-DI	Month 3: ACR20 HAQ-DI DAS28-4(ESR)<2.6	Month 6: mTSS ACR70	Month 6: ACR50



Time of mandatory placebo rescue to tofacitinib 5 or 10 mg twice daily	Month 3	Month 6 (placebo subjects with < 20% improvement in swollen and tender joint counts advanced to tofacitinib at month 3)	Month 3	NA	NA
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<sup>a</sup>. ≤3 weekly doses (MTX-naïve).

<sup>b</sup>. Antimalarials were allowed.

<sup>c</sup>. Co-primary endpoints as follows: mean change from baseline in mTSS; percent of subjects achieving ACR20 or ACR70 responses; mean change from baseline in HAQ-DI; percent of subjects achieving a DAS28-4(ESR) <2.6 (remission).

mTSS=modified Total Sharp Score, ACR20(70)=American College of Rheumatology ≥20% (≥70%) improvement, DAS28=Disease Activity Score 28 joints, ESR=Erythrocyte Sedimentation Rate, HAQ-DI=Health Assessment Questionnaire Disability Index, DMARD=disease-modifying antirheumatic drug, IR=inadequate responder, csDMARD=conventional synthetic DMARD, TNFi=tumour necrosis factor inhibitor, NA=not applicable, ADA=adalimumab, MTX=methotrexate.

Clinical response

*ACR response*

The percentages of tofacitinib-treated patients achieving ACR20, ACR50 and ACR70 responses in studies ORAL Solo, ORAL Sync, ORAL Standard, ORAL Scan, ORAL Step, ORAL Start, and ORAL Strategy are shown in Table 10. In all studies, patients treated with either 5 mg or 10 mg twice daily tofacitinib had statistically significant ACR20, ACR50 and ACR70 response rates at month 3 and month 6 versus placebo (or versus MTX in ORAL Start) treated patients.

Over the course of ORAL Strategy, responses with tofacitinib 5 mg twice daily + MTX were numerically similar compared to adalimumab 40 mg + MTX and both were numerically higher than tofacitinib 5 mg twice daily.



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

**Table 10: Proportion (%) of patients with an ACR response**

<b>ORAL Solo: DMARD inadequate responders</b>				
<b>Endpoint</b>	<b>Time</b>	<b>Placebo N=122</b>	<b>Tofacitinib 5 mg twice daily monotherapy N=241</b>	<b>Tofacitinib 10 mg twice daily monotherapy N=243</b>
ACR20	Month 3	26	60***	65***
	Month 6	NA	69	71
ACR50	Month 3	12	31***	37***
	Month 6	NA	42	47
ACR70	Month 3	6	15*	20***
	Month 6	NA	22	29
<b>ORAL Sync: DMARD inadequate responders</b>				
<b>Endpoint</b>	<b>Time</b>	<b>Placebo + DMARD(s) N=158</b>	<b>Tofacitinib 5 mg twice daily + DMARD(s) N=312</b>	<b>Tofacitinib 10 mg twice daily + DMARD(s) N=315</b>
ACR20	Month 3	27	56***	63***
	Month 6	31	53***	57***
	Month 12	NA	51	56



ACR50	Month 3	9	27***	33***
	Month 6	13	34***	36***
	Month 12	NA	33	42
ACR70	Month 3	2	8**	14***
	Month 6	3	13***	16***
	Month 12	NA	19	25

**ORAL Standard: MTX inadequate responders**

Endpoint	Time	Placebo N=105	Tofacitinib twice daily + Adalimumab 40 mg MTX		
			5 mg N=198	10 mg N=197	N=199
ACR20	Month 3	26	59***	57***	56***
	Month 6	28	51***	51***	46**
	Month 12	NA	48	49	48
ACR50	Month 3	7	33***	27***	24***
	Month 6	12	36***	34***	27**
	Month 12	NA	36	36	33
ACR70	Month 3	2	12**	15***	9*
	Month 6	2	19***	21***	9*
	Month 12	NA	22	23	17

**ORAL Scan: MTX inadequate responders**

Endpoint	Time	Placebo + MTX N=156	Tofacitinib 5 mg twice daily + MTX	
			N=316	Tofacitinib 10 mg twice daily + MTX N=309



ACR20	Month 3	27	55****	66****
	Month 6	25	50****	62****
	Month 12	NA	47	55
	Month 24	NA	40	50
ACR50	Month 3	8	28****	36****
	Month 6	8	32****	44****
	Month 12	NA	32	39
	Month 24	NA	28	40
ACR70	Month 3	3	10**	17****
	Month 6	1	14****	22****
	Month 12	NA	18	27
	Month 24	NA	17	26

**ORAL Step: TNF Inhibitor inadequate responders**

Endpoint	Time	Placebo + MTX N=132	Tofacitinib 5 mg twice daily + MTX N=133	Tofacitinib 10 mg twice daily + MTX N=134
ACR20	Month 3	24	41*	48****
	Month 6	NA	51	54
ACR50	Month 3	8	26****	28****
	Month 6	NA	37	30
ACR70	Month 3	2	14****	10*
	Month 6	NA	16	16

**ORAL Start: MTX-naïve**

Endpoint	Time	MTX	Tofacitinib 5 mg twice	Tofacitinib 10 mg twice
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		<b>N=184</b>	<b>daily monotherapy N=370</b>	<b>daily monotherapy N=394</b>
ACR20	Month 3	52	69***	77***
	Month 6	51	71***	75***
	Month 12	51	67**	71***
	Month 24	42	63***	64***
ACR50	Month 3	20	40***	49***
	Month 6	27	46***	56***
	Month 12	33	49**	55***
	Month 24	28	48***	49***
ACR70	Month 3	5	20***	26***
	Month 6	12	25***	37***
	Month 12	15	28**	38***
	Month 24	15	34***	37***
<b>ORAL Strategy: MTX inadequate responders</b>				
<b>Endpoint</b>	<b>Time</b>	<b>Tofacitinib 5 mg twice daily N=384</b>	<b>Tofacitinib 5 mg twice daily + MTX N=376</b>	<b>Adalimumab + MTX N=386</b>
ACR20	Month 3	62.50	70.48†	69.17
	Month 6	62.84	73.14†	70.98
	Month 12	61.72	70.21†	67.62
ACR50	Month 3	31.51	40.96†	37.31
	Month 6	38.28	46.01†	43.78
	Month 12	39.31	47.61†	45.85



ACR70	Month 3	13.54	19.41‡	14.51
	Month 6	18.23	25.00‡	20.73
	Month 12	21.09	28.99‡	25.91

\*p&lt;0.05

\*\*p&lt;0.001

\*\*\*p&lt;0.0001 versus placebo (versus MTX for ORAL Start)

‡p&lt;0.05 – tofacitinib 5 mg + MTX versus tofacitinib 5 mg for ORAL Strategy (normal p-values without multiple comparison adjustment)

QOW=every other week, N=number of subjects analysed, ACR20/50/70=American College of Rheumatology ≥20, 50, 70% improvement, NA=not applicable, MTX=methotrexate.

*DAS28-4(ESR) response*

Patients in the phase 3 studies had a mean Disease Activity Score (DAS28-4[ESR]) of 6.1-6.7 at baseline. Significant reductions in DAS28-4(ESR) from baseline (mean improvement) of 1.8-2.0 and 1.9-2.2 were observed in patients treated with 5 mg and 10 mg twice daily doses, respectively, compared to placebo-treated patients (0.7-1.1) at month 3. The proportion of patients achieving a DAS28 clinical remission (DAS28-4(ESR) < 2.6) in ORAL Step, ORAL Sync, and ORAL Standard is shown in Table 11.

**Table 11: Number (%) of subjects achieving DAS28-4(ESR) < 2.6 remission at months 3 and 6**

	Time Point	N	%
<b>ORAL Step: TNF Inhibitor inadequate responders</b>			
Tofacitinib 5 mg twice daily + MTX	Month 3	133	6
Tofacitinib 10 mg twice daily + MTX	Month 3	134	8*
Placebo + MTX	Month 3	132	2
<b>ORAL Sync: DMARD inadequate responders</b>			
Tofacitinib 5 mg twice daily	Month 6	312	8*



Tofacitinib 10 mg twice daily	Month 6	315	11***
Placebo	Month 6	158	3
<b>ORAL Standard: MTX inadequate responders</b>			
Tofacitinib 5 mg twice daily + MTX	Month 6	198	6*
Tofacitinib 10 mg twice daily + MTX	Month 6	197	11***
Adalimumab 40 mg SC QOW + MTX	Month 6	199	6*
Placebo + MTX	Month 6	105	1
*p <0.05, ***p<0.0001 versus placebo, SC=subcutaneous, QOW=every other week, N=number of subjects analysed, DAS28=Disease Activity Scale 28 joints, ESR=Erythrocyte Sedimentation Rate.			

#### *Radiographic response*

In ORAL Scan and ORAL Start, inhibition of progression of structural joint damage was assessed radiographically and expressed as mean change from baseline in mTSS and its components, the erosion score and joint space narrowing (JSN) score, at months 6 and 12.

In ORAL Scan, tofacitinib 10 mg twice daily plus background MTX resulted in significantly greater inhibition of the progression of structural damage compared to placebo plus MTX at months 6 and 12. When given at a dose of 5 mg twice daily, tofacitinib plus MTX exhibited similar effects on mean progression of structural damage (not statistically significant). Analysis of erosion and JSN scores were consistent with overall results.

In the placebo plus MTX group, 78% of patients experienced no radiographic progression (mTSS change less than or equal to 0.5) at month 6 compared to 89% and 87% of patients treated with tofacitinib 5 or 10 mg (plus MTX) twice daily respectively, (both significant versus placebo plus MTX).

In ORAL Start, tofacitinib monotherapy resulted in significantly greater inhibition of the progression of structural damage compared to MTX at months 6 and 12 as shown in Table 12, which was also maintained at month 24. Analyses of erosion and JSN scores were consistent with overall results.



In the MTX group, 70% of patients experienced no radiographic progression at month 6 compared to 83% and 90% of patients treated with tofacitinib 5 or 10 mg twice daily respectively, both significant versus MTX.

**Table 12: Radiographic changes at months 6 and 12**

<b>ORAL Scan: MTX inadequate responders</b>					
	<b>Placebo + MTX N=139 Mean (SD)<sup>a</sup></b>	<b>Tofacitinib 5 mg twice daily + MTX N=277 Mean (SD)<sup>a</sup></b>	<b>Tofacitinib 5 mg twice daily + MTX Mean difference from placebo<sup>b</sup> (CI)</b>	<b>Tofacitinib 10 mg twice daily + MTX N=290 Mean (SD)<sup>a</sup></b>	<b>Tofacitinib 10 mg twice daily + MTX Mean difference from placebo<sup>b</sup> (CI)</b>
mTSS <sup>c</sup>					
Baseline	33 (42)	31 (48)	-	37 (54)	-
Month 6	0.5 (2.0)	0.1 (1.7)	-0.3 (-0.7, 0.0)	0.1 (2.0)	-0.4 (-0.8, 0.0)
Month 12	1.0 (3.9)	0.3 (3.0)	-0.6 (-1.3, 0.0)	0.1 (2.9)	-0.9 (-1.5, -0.2)
<b>ORAL Start: MTX-naïve</b>					
	<b>MTX N=168 Mean (SD)<sup>a</sup></b>	<b>Tofacitinib 5 mg twice daily N=344 Mean (SD)<sup>a</sup></b>	<b>Tofacitinib 5 mg twice daily Mean difference from MTX<sup>d</sup> (CI)</b>	<b>Tofacitinib 10 mg twice daily N=368 Mean (SD)<sup>a</sup></b>	<b>Tofacitinib 10 mg twice daily Mean difference from MTX<sup>d</sup> (CI)</b>
mTSS <sup>c</sup>					
Baseline	16 (29)	20 (41)	-	19 (39)	-
Month 6	0.9 (2.7)	0.2 (2.3)	-0.7 (-1.0, -0.3)	0.0 (1.2)	-0.8 (-1.2, -0.4)
Month 12	1.3 (3.7)	0.4 (3.0)	-0.9 (-1.4, -0.4)	0.0 (1.5)	-1.3 (-1.8, -0.8)
<sup>a</sup> SD = Standard Deviation					
<sup>b</sup> Difference between least squares means tofacitinib minus placebo (95% CI = 95% confidence interval)					
<sup>c</sup> Month 6 and month 12 data are mean change from baseline					
<sup>d</sup> Difference between least squares means tofacitinib minus MTX (95% CI = 95% confidence interval)					



*Physical function response and health-related outcomes*

Tofacitinib, alone or in combination with MTX, has shown improvements in physical function, as measured by the HAQ-DI. Patients receiving tofacitinib 5 or 10 mg twice daily demonstrated significantly greater improvement from baseline in physical functioning compared to placebo at month 3 (studies ORAL Solo, ORAL Sync, ORAL Standard, and ORAL Step) and month 6 (studies ORAL Sync and ORAL Standard). Tofacitinib 5 or 10 mg twice daily-treated patients demonstrated significantly greater improvement in physical functioning compared to placebo as early as week 2 in ORAL Solo and ORAL Sync. Changes from baseline in HAQ-DI in studies ORAL Standard, ORAL Step and ORAL Sync are shown in Table 13.

**Table 13: LS mean change from baseline in HAQ-DI at month 3**

	Placebo + MTX	Tofacitinib 5 mg twice daily + MTX	Tofacitinib 10 mg twice daily + MTX	Adalimumab 40 mg QOW + MTX
<b>ORAL Standard: MTX inadequate responders</b>				
	N=96	N=185	N=183	N=188
	-0.24	-0.54***	-0.61***	-0.50***
<b>ORAL Step: TNF inhibitor inadequate responders</b>				
	N=118	N=117	N=125	NA
	-0.18	-0.43***	-0.46***	NA
	Placebo + DMARD(s)	Tofacitinib 5 mg twice daily + DMARD(s)	Tofacitinib 10 mg twice daily + DMARD(s)	
<b>ORAL Sync: DMARD inadequate responders</b>				
	N=147	N=292	N=292	NA
	-0.21	-0.46***	-0.56***	NA



\*\*\*  $p < 0.0001$ , tofacitinib versus placebo + MTX, LS = least squares, N = number of patients, QOW = every other week, NA = not applicable, HAQ-DI = Health Assessment Questionnaire Disability Index

Health-related quality of life was assessed by the Short Form Health Survey (SF-36). Patients receiving either 5 or 10 mg tofacitinib twice daily experienced significantly greater improvement from baseline compared to placebo in all 8 domains as well as the Physical Component Summary and Mental Component Summary scores at month 3 in ORAL Solo, ORAL Scan and ORAL Step. In ORAL Scan, mean SF-36 improvements were maintained to 12 months in tofacitinib-treated patients.

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

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

#### Durability of clinical responses

Durability of effect was assessed by ACR20, ACR50, ACR70 response rates in studies of duration of up to two years. Changes in mean HAQ-DI and DAS28-4(ESR) were maintained in both tofacitinib treatment groups through to the end of the studies.

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

**MICRO LABS LIMITED, INDIA**  
**SUMMARY OF PRODUCT CHARACTERISTICS**  
**TOFACITINIB TABLET 5 mg (JITRIT)**

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Long-term controlled safety data

Study ORAL Surveillance (A3921133) was a large (N=4362), randomised active-controlled post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular risk factor (CV risk factors defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g. nodules, Sjögren's syndrome, anaemia of chronic disease, pulmonary manifestations). Patients were required to be on a stable dose of methotrexate at study entry; dose adjustment was permitted during the study.

Patients were randomised to open-label tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, or a TNF inhibitor (TNF inhibitor was either etanercept 50 mg once weekly or adalimumab 40 mg every other week) in a 1:1:1 ratio. The co-primary endpoints were adjudicated malignancies excluding NMSC and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessment of endpoints were blinded. The study was an event-powered study that also required at least 1500 patients to be followed for 3 years. The study treatment of tofacitinib 10 mg twice daily was stopped and patients were switched to 5 mg twice daily because of a dose-dependent signal of venous thromboembolic events (VTE). For patients in the tofacitinib 10 mg twice daily treatment arm, the data collected before and after the dose switch were analysed in their originally randomised treatment group.

The study did not meet the non-inferiority criterion for the primary comparison of the combined tofacitinib doses to TNF inhibitor since the upper limit of the 95% CI for HR exceeded the pre-specified non-inferiority criterion of 1.8 for adjudicated MACE and adjudicated malignancies excluding NMSC.

Final results are provided below for MACE, myocardial infarction, malignancies excluding NMSC, lung cancer and lymphoma for each randomised treatment arm. Interim safety analysis (2019) results are provided for VTE, serious infections, and mortality.



MACE (including myocardial infarction)

An increase in non-fatal myocardial infarction was observed in patients treated with tofacitinib compared to TNF inhibitor.

**Table 14: Incidence rate and hazard ratio for MACE and myocardial infarction**

	Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily <sup>a</sup>	All Tofacitinib <sup>b</sup>	TNF inhibitor (TNFi)
<b>MACE<sup>c</sup></b>				
IR (95% CI) per 100 PY	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.98 (0.79, 1.19)	0.73 (0.52, 1.01)
HR (95% CI) vs TNFi	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)	
<b>Fatal MI<sup>c</sup></b>				
IR (95% CI) per 100 PY	0.00 (0.00, 0.07)	0.06 (0.01, 0.18)	0.03 (0.01, 0.09)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	0.00 (0.00, Inf)	1.03 (0.21, 5.11)	0.50 (0.10, 2.49)	
<b>Non-fatal MI<sup>c</sup></b>				
IR (95% CI) per 100 PY	0.37 (0.22, 0.57)	0.33 (0.19, 0.53)	0.35 (0.24, 0.48)	0.16 (0.07, 0.31)
HR (95% CI) vs TNFi	2.32 (1.02, 5.30)	2.08 (0.89, 4.86)	2.20 (1.02, 4.75)	
<sup>a</sup> The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification. <sup>b</sup> Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily. <sup>c</sup> Based on events occurring on treatment or within 60 days of treatment discontinuation. Abbreviations: MACE = major adverse cardiovascular events, MI = myocardial infarction, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, Inf = infinity				

The following predictive factors for development of MI (fatal and non-fatal) were identified using a multivariate Cox model with backward selection: age  $\geq$  65 years, male, current or past



smoking, history of diabetes, and history of coronary artery disease (which includes myocardial infarction, coronary heart disease, stable angina pectoris, or coronary artery procedures) (see section 4.4 and 4.8).

Malignancies

An increase in malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed in patients treated with tofacitinib compared to TNF inhibitor.

**Table 15: Incidence rate and hazard ratio for malignancies excluding NMSC<sup>a</sup>**

	<b>Tofacitinib 5 mg twice daily</b>	<b>Tofacitinib 10 mg twice daily<sup>b</sup></b>	<b>All Tofacitinib<sup>c</sup></b>	<b>TNF inhibitor (TNFi)</b>
<b>Malignancies excluding NMSC</b>				
IR (95% CI) per 100 PY	1.13 (0.87, 1.45)	1.13 (0.86, 1.45)	1.13 (0.94, 1.35)	0.77 (0.55, 1.04)
HR (95% CI) vs TNFi	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)	
<b>Lung cancer</b>				
IR (95% CI) per 100 PY	0.23 (0.12, 0.40)	0.32 (0.18, 0.51)	0.28 (0.19, 0.39)	0.13 (0.05, 0.26)
HR (95% CI) vs TNFi	1.84 (0.74, 4.62)	2.50 (1.04, 6.02)	2.17 (0.95, 4.93)	
<b>Lymphoma</b>				
IR (95% CI) per 100 PY	0.07 (0.02, 0.18)	0.11 (0.04, 0.24)	0.09 (0.04, 0.17)	0.02 (0.00, 0.10)
HR (95% CI) vs TNFi	3.99 (0.45, 35.70)	6.24 (0.75, 51.86)	5.09 (0.65, 39.78)	
<sup>a</sup> Based on events occurring on treatment or after treatment discontinuation up to the end of the study				
<sup>b</sup> The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.				
<sup>c</sup> Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.				



Abbreviations: NMSC = non melanoma skin cancer, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years

The following predictive factors for development of malignancies excluding NMSC were identified using a Multivariate Cox model with backward selection: age  $\geq$  65 years and current or past smoking (see section 4.4 and 4.8).

#### Venous thromboembolism (VTE)

In an interim analysis of study A3921133, an increased and dose-dependent incidence of VTE was observed in patients treated with tofacitinib compared to TNF inhibitors (see section 4.8). The majority of these events were serious and some cases of PE resulted in death. The incidence rates (95% CI) for PE for tofacitinib 10 mg twice daily, 5 mg twice daily, and TNF inhibitors were 0.54 (0.32-0.87), 0.27 (0.12-0.52), and 0.09 (0.02-0.26) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the HR for PE with tofacitinib 10 mg twice daily was 5.96 (1.75-20.33), and for 5 mg twice daily the HR was 2.99 (0.81-11.06). The incidence rates (95% CI) for DVT for tofacitinib 10 mg twice daily, 5 mg twice daily, and TNF inhibitors were 0.38 (0.20-0.67), 0.30 (0.14-0.55), and 0.18 (0.07-0.39) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the HR for DVT with tofacitinib 10 mg twice daily was 2.13 (0.80-5.69), and for 5 mg twice daily the HR was 1.66 (0.60-4.57).

#### Mortality

In an interim analysis of study A3921133, increased mortality within 28 days of last treatment was observed in patients treated with tofacitinib compared to TNF inhibitors. The incidence rates (95% CI) were 0.89 (0.59-1.29) for tofacitinib 10 mg twice daily, 0.57 (0.34-0.89) for tofacitinib 5 mg twice daily, and 0.27 (0.12-0.51) for TNF-inhibitors; with a HR (95% CI) of 3.28 (1.55-6.95) for tofacitinib 10 mg twice daily and of 2.11 (0.96-4.67) for tofacitinib 5 mg twice daily, versus TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies.

For cardiovascular mortality within 28 days of last treatment, the incidence rates (95% CI) per 100 patients-years were 0.45 (0.24-0.75) for tofacitinib 10 mg twice daily, 0.24 (0.10-0.47) for



tofacitinib 5 mg twice daily, and 0.21 (0.08-0.43) for TNF inhibitors; with an incident rate ratio (IRR) (95% CI) of 2.12 (0.80-6.20) for tofacitinib 10 mg twice daily and of 1.14 (0.36-3.70) for tofacitinib 5 mg twice daily, versus TNF inhibitors.

For fatal infections within 28 days of last treatment, the incidence rates per 100 patient-years (95% CI) were 0.22 (0.09-0.46), 0.18 (0.07-0.39), and 0.06 (0.01-0.22) for tofacitinib 10 mg twice daily and 5 mg twice daily, and TNF inhibitors, respectively; with an IRR (95% CI) of 3.70 (0.71-36.5) for 10 mg twice daily and of 3.00 (0.54-30.4) for tofacitinib 5 mg twice daily, versus TNF inhibitors.

#### Serious infections

In an interim analysis, for non-fatal serious infections, the incidence rates (95% CI) per 100 patient-years were 3.51 (2.93-4.16), 3.35 (2.78-4.01), and 2.79 (2.28-3.39), for tofacitinib 10 mg and 5 mg twice daily and TNF inhibitors, respectively. The risk of serious (fatal and non-fatal) infections was further increased in patients over 65 years of age, as compared to younger patients in study A3921133.

#### Psoriatic arthritis

The efficacy and safety of tofacitinib film-coated tablets were assessed in 2 randomised, double-blind, placebo-controlled Phase 3 studies in adult patients with active PsA ( $\geq 3$  swollen and  $\geq 3$  tender joints). Patients were required to have active plaque psoriasis at the screening visit. For both studies, the primary endpoints were ACR20 response rate and change from baseline in HAQ-DI at month 3.

Study PsA-I (OPAL BROADEN) evaluated 422 patients who had a previous inadequate response (due to lack of efficacy or intolerance) to a csDMARD (MTX for 92.7% of patients); 32.7% of the patients in this study had a previous inadequate response to  $> 1$  csDMARD or 1 csDMARD and a targeted synthetic DMARD (tsDMARD). In OPAL BROADEN, previous treatment with TNF inhibitor was not allowed. All patients were required to have 1 concomitant csDMARD; 83.9% of patients received concomitant MTX, 9.5% of patients received



concomitant sulfasalazine, and 5.7% of patients received concomitant leflunomide. The median PsA disease duration was 3.8 years. At baseline, 79.9% and 56.2% of patients had enthesitis and dactylitis, respectively. Patients randomised to tofacitinib received 5 mg twice daily or tofacitinib 10 mg twice daily for 12 months. Patients randomised to placebo were advanced in a blinded manner at month 3 to either tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily and received treatment until month 12. Patients randomised to adalimumab (active-control arm) received 40 mg subcutaneously every 2 weeks for 12 months.

Study PsA-II (OPAL BEYOND) evaluated 394 patients who had discontinued a TNF inhibitor due to lack of efficacy or intolerance; 36.0% had a previous inadequate response to > 1 biological DMARD. All patients were required to have 1 concomitant csDMARD; 71.6% of patients received concomitant MTX, 15.7% of patients received concomitant sulfasalazine, and 8.6% of patients received concomitant leflunomide. The median PsA disease duration was 7.5 years. At baseline, 80.7% and 49.2% of patients had enthesitis and dactylitis, respectively. Patients randomised to tofacitinib received 5 mg twice daily or tofacitinib 10 mg twice daily for 6 months. Patients randomised to placebo were advanced in a blinded manner at month 3 to either tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily and received treatment until month 6.

*Signs and symptoms*

Treatment with tofacitinib resulted in significant improvements in some signs and symptoms of PsA, as assessed by the ACR20 response criteria compared to placebo at month 3. The efficacy results for important endpoints assessed are shown in Table 16.

**Table 16: Proportion (%) of PsA patients who achieved clinical response and mean change from baseline in OPAL BROADEN and OPAL BEYOND studies**

	Conventional synthetic DMARD inadequate responders <sup>a</sup> (TNFi-naïve)	TNFi inadequate responders <sup>b</sup>
	<b>OPAL BROADEN</b>	<b>OPAL BEYOND<sup>c</sup></b>



Treatment group	Placebo	Tofacitinib 5 mg twice daily	Adalimumab 40 mg SC q2W	Placebo	Tofacitinib 5 mg twice daily
N	105	107	106	131	131
ACR20					
Month 3	33%	50% <sup>d,*</sup>	52% <sup>*</sup>	24%	50% <sup>d,***</sup>
Month 6	NA	59%	64%	NA	60%
Month 12	NA	68%	60%	-	-
ACR50					
Month 3	10%	28% <sup>e,**</sup>	33% <sup>***</sup>	15%	30% <sup>e,*</sup>
Month 6	NA	38%	42%	NA	38%
Month 12	NA	45%	41%	-	-
ACR70					
Month 3	5%	17% <sup>e,*</sup>	19% <sup>*</sup>	10%	17%
Month 6	NA	18%	30%	NA	21%
Month 12	NA	23%	29%	-	-
$\Delta$ LEI <sup>f</sup>					
Month 3	-0.4	-0.8	-1.1 <sup>*</sup>	-0.5	-1.3 <sup>*</sup>
Month 6	NA	-1.3	-1.3	NA	-1.5
Month 12	NA	-1.7	-1.6	-	-
$\Delta$ DSS <sup>f</sup>					
Month 3	-2.0	-3.5	-4.0	-1.9	-5.2 <sup>*</sup>
Month 6	NA	-5.2	-5.4	NA	-6.0
Month 12	NA	-7.4	-6.1	-	-
PASI75 <sup>g</sup>					
Month 3	15%	43% <sup>d,***</sup>	39% <sup>**</sup>	14%	21%
Month 6	NA	46%	55%	NA	34%
Month 12	NA	56%	56%	-	-



\* Nominal  $p \leq 0.05$ ; \*\* Nominal  $p < 0.001$ ; \*\*\* Nominal  $p < 0.0001$  for active treatment versus placebo at month 3.

Abbreviations: BSA=body surface area;  $\Delta$ LEI=change from baseline in Leeds Enthesitis Index;  $\Delta$ DSS=change from baseline in Dactylitis Severity Score; ACR20/50/70=American College of Rheumatology  $\geq 20\%$ ,  $50\%$ ,  $70\%$  improvement; csDMARD=conventional synthetic disease-modifying antirheumatic drug; N=number of randomised and treated patients; NA=Not applicable, as data for placebo treatment is not available beyond month 3 due to placebo advanced to tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily; SC q2w=subcutaneously once every 2 weeks; TNFi=tumour necrosis factor inhibitor; PASI=Psoriasis Area and Severity index; PASI75= $\geq 75\%$  improvement in PASI.

<sup>a</sup> Inadequate response to at least 1 csDMARD due to lack of efficacy and/or intolerability.

<sup>b</sup> Inadequate response to a least 1 TNFi due to lack of efficacy and/or intolerability.

<sup>c</sup> OPAL BEYOND had a duration of 6 months.

<sup>d</sup> Achieved statistical significance globally at  $p \leq 0.05$  per the pre-specified step-down testing procedure.

<sup>e</sup> Achieved statistical significance within the ACR family (ACR50 and ACR70) at  $p \leq 0.05$  per the pre-specified step-down testing procedure.

<sup>f</sup> For patients with Baseline score  $> 0$ .

<sup>g</sup> For patients with Baseline BSA  $\geq 3\%$  and PASI  $> 0$ .

Both TNF inhibitor naïve and TNF inhibitor inadequate responder tofacitinib 5 mg BID -treated patients had significantly higher ACR20 response rates compared to placebo at month 3. Examination of age, sex, race, baseline disease activity and PsA subtype did not identify differences in response to tofacitinib. The number of patients with arthritis mutilans or axial involvement was too small to allow meaningful assessment. Statistically significant ACR20 response rates were observed with tofacitinib 5 mg BID in both studies as early as week 2 (first post-baseline assessment) in comparison to placebo.

In OPAL BROADEN, Minimal Disease Activity (MDA) response was achieved by 26.2%, 25.5% and 6.7% of tofacitinib 5 mg BID, adalimumab and placebo treated patients, respectively (tofacitinib 5 mg BID treatment difference from placebo 19.5% [95% CI: 9.9, 29.1]) at month 3.



In OPAL BEYOND, MDA was achieved by 22.9% and 14.5% of tofacitinib 5 mg BID and placebo treated patients, respectively, however tofacitinib 5 mg BID did not achieve nominal statistical significance (treatment difference from placebo 8.4% [95% CI: -1.0, 17.8] at month 3).

#### *Radiographic response*

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

#### *Physical function and health-related quality of life*

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving tofacitinib 5 mg twice daily demonstrated greater improvement ( $p \leq 0.05$ ) from baseline in physical functioning compared to placebo at month 3 (see Table 17).

**Table 17: Change from baseline in HAQ-DI in PsA studies OPAL BROADEN and OPAL BEYOND**

	Least squares mean change from baseline in HAQ-DI				
	Conventional synthetic DMARD inadequate responders <sup>a</sup> (TNFi-naïve)			TNFi inadequate responders <sup>b</sup>	
	OPAL BROADEN			OPAL BEYOND	
Treatment group	Placebo	Tofacitinib 5 mg twice daily	Adalimumab 40 mg SC q2W	Placebo	Tofacitinib 5 mg twice daily
N	104	107	106	131	129
Month 3	-0.18	-0.35 <sup>c,*</sup>	-0.38 <sup>*</sup>	-0.14	-0.39 <sup>c,***</sup>
Month 6	NA	-0.45	-0.43	NA	-0.44



Month 12	NA	-0.54	-0.45	NA	NA
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\* Nominal  $p \leq 0.05$ ; \*\*\* Nominal  $p < 0.0001$  for active treatment versus placebo at month 3.

Abbreviations: DMARD=disease-modifying antirheumatic drug; HAQ-DI=Health Assessment Questionnaire Disability Index; N=total number of patients in the statistical analysis; SC q2w=subcutaneously once every 2 weeks; TNFi=tumour necrosis factor inhibitor.

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

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

<sup>c</sup> Achieved statistical significance globally at  $p \leq 0.05$  per the pre-specified step-down testing procedure.

The HAQ-DI responder rate (response defined as having decrease from baseline of  $\geq 0.35$ ) at month 3 in studies OPAL BROADEN and OPAL BEYOND was 53% and 50%, respectively in patients receiving tofacitinib 5 mg twice daily, 31% and 28%, respectively in patients receiving placebo, and 53% in patients receiving adalimumab 40 mg subcutaneously once every 2 weeks (OPAL BROADEN only).

Health-related quality of life was assessed by SF-36v2, fatigue was assessed by the FACIT-F. Patients receiving tofacitinib 5 mg twice daily demonstrated greater improvement from baseline compared to placebo in the SF-36v2 physical functioning domain, the SF-36v2 physical component summary score, and FACIT-F scores at month 3 in studies OPAL BROADEN and OPAL BEYOND (nominal  $p \leq 0.05$ ). Improvements from baseline in SF-36v2 and FACIT-F were maintained through month 6 (OPAL BROADEN and OPAL BEYOND) and month 12 (OPAL BROADEN).

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



### Ankylosing spondylitis

The tofacitinib clinical development program to assess the efficacy and safety included one placebo-controlled confirmatory trial (Study AS-I). Study AS-I was a randomised, double-blind, placebo-controlled, 48-week treatment clinical trial in 269 adult patients who had an inadequate response (inadequate clinical response or intolerance) to at least 2 NSAIDs. Patients were randomised and treated with tofacitinib 5 mg twice daily or placebo for 16 weeks of blinded treatment and then all were advanced to tofacitinib 5 mg twice daily for an additional 32 weeks. 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 DMARD therapy.

Approximately 7% and 21% of patients used concomitant methotrexate or sulfasalazine, respectively, from baseline to Week 16. Patients were allowed to receive a stable low dose of oral corticosteroids (8.6% received) and/or NSAIDs (81.8% received) from baseline to Week 48. Twenty-two percent of patients had an inadequate response to 1 or 2 TNF blockers. The primary endpoint was to evaluate the proportion of patients who achieved an ASAS20 response at Week 16.

### 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 18). The responses were maintained from Week 16 through to Week 48 in patients receiving tofacitinib 5 mg twice daily.

**Table 18: ASAS20 and ASAS40 Responses at Week 16, Study AS-I**

	<b>Placebo (N=136)</b>	<b>Tofacitinib 5 mg Twice Daily (N=133)</b>	<b>Difference from Placebo (95% CI)</b>
ASAS20 response*, %	29	56	27 (16, 38)**
ASAS40 response*, %	13	41	28 (18, 38)**

\* type I error-controlled.



\*\* p < 0.0001.

The efficacy of tofacitinib was demonstrated in bDMARD naïve and TNF-inadequate responders (IR)/bDMARD experienced (non-IR) patients (Table 19).

**Table 19. ASAS20 and ASAS40 Responses (%) by Treatment History at Week 16, Study AS-I**

Prior Treatment History	Efficacy Endpoint					
	ASAS20			ASAS40		
	Placebo N	Tofacitinib 5 mg Twice Daily N	Difference from Placebo (95% CI)	Placebo N	Tofacitinib 5 mg Twice Daily N	Difference from Placebo (95% CI)
bDMARD-Naïve	105	102	28 (15, 41)	105	102	31 (19, 43)
TNFi-IR or bDMARD Use (Non-IR)	31	31	23 (1, 44)	31	31	19 (2, 37)

ASAS20 = An improvement from Baseline  $\geq 20\%$  and  $\geq 1$  unit increase in at least 3 domains on a scale of 0 to 10, and no worsening of  $\geq 20\%$  and  $\geq 1$  unit in the remaining domain; ASAS40 = An improvement from Baseline  $\geq 40\%$  and  $\geq 2$  units in at least 3 domains on a scale of 0 to 10 and no worsening at all in the remaining domain; bDMARD = biologic disease-modifying anti-rheumatic drug; CI = confidence interval; Non-IR = non-inadequate response; TNFi-IR = tumour 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 at Week 16 as shown in Table 20. The improvements were maintained from Week 16 through to Week 48 in patients receiving tofacitinib 5 mg twice daily.

**Table 20: ASAS Components and Other Measures of Disease Activity at Week 16, Study AS-I**



	Placebo (N=136)		Tofacitinib 5 mg Twice Daily (N=133)		Difference from Placebo (95% CI)
	Baseline (mean)	Week 16 (LSM change from Baseline)	Baseline (mean)	Week 16 (LSM change from Baseline)	
ASAS Components					
- Patient Global Assessment of Disease Activity (0- 10) <sup>a,*</sup>	7.0	-0.9	6.9	-2.5	-1.6 (-2.07, -1.05)**
- Total spinal pain (0-10) <sup>a,*</sup>	6.9	-1.0	6.9	-2.6	-1.6 (-2.10, -1.14)**
- BASFI (0-10) <sup>b,*</sup>	5.9	-0.8	5.8	-2.0	-1.2 (-1.66, -0.80)**
- Inflammation (0- 10) <sup>c,*</sup>	6.8	-1.0	6.6	-2.7	-1.7 (-2.18, -1.25)**
BASDAI Score <sup>d</sup>	6.5	-1.1	6.4	-2.6	-1.4 (-1.88, -1.00)**
BASMI <sup>e,*</sup>	4.4	-0.1	4.5	-0.6	-0.5 (-0.67, -0.37)**
hsCRP <sup>f,*</sup> (mg/dL)	1.8	-0.1	1.6	-1.1	-1.0 (-1.20, -0.72)**
ASDAScrp <sup>g,*</sup>	3.9	-0.4	3.8	-1.4	-1.0 (-1.16, -0.79)**
* type I error-controlled.					
** p < 0.0001.					



<sup>a</sup> Measured on a numerical rating scale with 0 = not active or no pain, 10 = very active or most severe pain.

<sup>b</sup> Bath Ankylosing Spondylitis Functional Index measured on a numerical rating scale with 0 = easy and 10 = impossible.

<sup>c</sup> Inflammation is the mean of two patient-reported stiffness self-assessments in BASDAI.

<sup>d</sup> Bath Ankylosing Spondylitis Disease Activity Index total score.

<sup>e</sup> Bath Ankylosing Spondylitis Metrology Index.

<sup>f</sup> High sensitivity C-reactive protein.

<sup>g</sup> Ankylosing Spondylitis Disease Activity Score with C-reactive protein.

LSM = least squares mean

#### 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) and Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Total score (6.5 vs 3.1) compared to placebo-treated patients at Week 16 ( $p < 0.001$ ). Patients treated with tofacitinib 5 mg twice daily achieved consistently greater improvements from baseline in the Short Form health survey version 2 (SF-36v2), Physical Component Summary (PCS) domain compared to placebo-treated patients at Week 16.

#### *Ulcerative colitis*

The efficacy and safety of tofacitinib film-coated tablets for the treatment of adult patients with moderately to severely active UC (Mayo score 6 to 12 with endoscopy subscore  $\geq 2$  and rectal bleeding subscore  $\geq 1$ ) were assessed in 3 multicentre, double-blind, randomised, placebo-controlled studies: 2 identical induction studies (OCTAVE Induction 1 and OCTAVE Induction 2) followed by 1 maintenance study (OCTAVE Sustain). Enrolled patients had failed at least 1 conventional therapy, including corticosteroids, immunomodulators, and/or a TNF inhibitor. Concomitant stable doses of oral aminosalicylates and corticosteroids (prednisone or equivalent daily dose up to 25 mg) were permitted with taper of corticosteroids to discontinuation mandated



within 15 weeks of entering the maintenance study. Tofacitinib was administered as monotherapy (i.e., without concomitant use of biologics and immunosuppressants) for UC.

Table 21 provides additional information regarding pertinent study design and population characteristics.

**Table 21: Phase 3 clinical studies of tofacitinib 5 mg and 10 mg twice daily doses in patients with UC**

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



immunosuppressant failure			
Baseline corticosteroid use	45.5%	46.8%	50.3%
Abbreviations: TNFi=tumour necrosis factor inhibitor; UC=ulcerative colitis.			

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

*Induction efficacy data (OCTAVE Induction 1 and OCTAVE Induction 2)*

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

A significantly greater proportion of patients treated with tofacitinib 10 mg twice daily achieved remission, improvement of endoscopic appearance of the mucosa, and clinical response at week 8 compared to placebo in both studies, as shown in Table 22.

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

**Table 22: Proportion of patients meeting efficacy endpoints at week 8 (OCTAVE induction study 1 and OCTAVE induction study 2)**



Endpoint	OCTAVE induction study 1			
	Central endoscopy read		Local endoscopy read	
	Placebo	Tofacitinib 10 mg twice daily	Placebo	Tofacitinib 10 mg twice daily
	N=122	N=476	N=122	N=476
Remission <sup>a</sup>	8.2%	18.5% <sup>‡</sup>	11.5%	24.8% <sup>‡</sup>
Improvement of endoscopic appearance of the mucosa <sup>b</sup>	15.6%	31.3% <sup>†</sup>	23.0%	42.4% <sup>*</sup>
Normalisation of endoscopic appearance of the mucosa <sup>c</sup>	1.6%	6.7% <sup>‡</sup>	2.5%	10.9% <sup>‡</sup>
Clinical response <sup>d</sup>	32.8%	59.9% <sup>*</sup>	34.4%	60.7% <sup>*</sup>
Endpoint	OCTAVE induction study 2			
	Central endoscopy read		Local endoscopy read	
	Placebo	Tofacitinib 10 mg twice daily	Placebo	Tofacitinib 10 mg twice daily
	N=112	N=429	N=112	N=429
Remission <sup>a</sup>	3.6%	16.6% <sup>†</sup>	5.4%	20.7% <sup>†</sup>
Improvement of endoscopic appearance of the mucosa <sup>b</sup>	11.6%	28.4% <sup>†</sup>	15.2%	36.4% <sup>*</sup>
Normalisation of endoscopic appearance of the mucosa <sup>c</sup>	1.8%	7.0% <sup>‡</sup>	0.0%	9.1% <sup>‡</sup>
Clinical response <sup>d</sup>	28.6%	55.0% <sup>*</sup>	29.5%	58.0% <sup>*</sup>

\* p<0.0001; † p<0.001; ‡ p<0.05.

N=number of patients in the analysis set.

<sup>a</sup>. Primary endpoint: Remission was defined as clinical remission (a Mayo score ≤ 2 with no individual



subscore > 1) and rectal bleeding subscore of 0.

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

<sup>c</sup>. Normalisation of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0.

<sup>d</sup>. Clinical response was defined as a decrease from baseline in Mayo score of  $\geq 3$  points and  $\geq 30\%$ , with an accompanying decrease in the subscore for rectal bleeding of  $\geq 1$  point or absolute subscore for rectal bleeding of 0 or 1.

In both subgroups of patients with or without prior TNF inhibitor failure, a greater proportion of patients treated with tofacitinib 10 mg twice daily achieved remission and improvement of endoscopic appearance of the mucosa at week 8 as compared to placebo. This treatment difference was consistent between the 2 subgroups (Table 23).

**Table 23. Proportion of patients meeting primary and key secondary efficacy endpoints at week 8 by TNF inhibitor therapy subgroups (OCTAVE induction study 1 and OCTAVE induction study 2, central endoscopy read)**

<b>OCTAVE induction study 1</b>		
<b>Endpoint</b>	<b>Placebo N=122</b>	<b>Tofacitinib 10 mg twice daily N=476</b>
<b>Remission<sup>a</sup></b>		
With prior TNF inhibitor failure	1.6% (1/64)	11.1% (27/243)
Without prior TNF inhibitor failure <sup>b</sup>	15.5% (9/58)	26.2% (61/233)
<b>Improvement of endoscopic appearance of the mucosa<sup>c</sup></b>		
With prior TNF inhibitor failure	6.3% (4/64)	22.6% (55/243)
Without prior TNF inhibitor failure <sup>b</sup>	25.9%	40.3%

**MICRO LABS LIMITED, INDIA**  
**SUMMARY OF PRODUCT CHARACTERISTICS**  
**TOFACITINIB TABLET 5 mg (JITRIT)**



	(15/58)	(94/233)
<b>OCTAVE induction study 2</b>		
<b>Endpoint</b>	<b>Placebo</b>	<b>Tofacitinib 10 mg twice daily</b>
	<b>N=112</b>	<b>N=429</b>
Remission <sup>a</sup>		
With prior TNF inhibitor failure	0.0%	11.7%
	(0/60)	(26/222)
Without prior TNF inhibitor failure <sup>b</sup>	7.7%	21.7%
	(4/52)	(45/207)
Improvement of endoscopic appearance of the mucosa <sup>c</sup>		
With prior TNF inhibitor failure	6.7%	21.6%
	(4/60)	(48/222)
Without prior TNF inhibitor failure <sup>b</sup>	17.3%	35.7%
	(9/52)	(74/207)
TNF=tumour necrosis factor; N=number of patients in the analysis set.		
<sup>a</sup> Remission was defined as clinical remission (a Mayo score $\leq 2$ with no individual subscore $> 1$ ) and rectal bleeding subscore of 0.		
<sup>b</sup> Included TNF Inhibitor naïve patients		
<sup>c</sup> Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).		

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

Maintenance (OCTAVE Sustain)



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

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

A significantly greater proportion of patients in both the tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily treatment groups achieved the following endpoints at week 52 as compared to placebo: remission, improvement of endoscopic appearance of the mucosa, normalisation of endoscopic appearance of the mucosa, maintenance of clinical response, remission among patients in remission at baseline, and sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline, as shown in Table 24.

<b>Table 24: Proportion of patients meeting efficacy endpoints at week 52 (OCTAVE sustain)</b>						
<b>Endpoint</b>	<b>Central endoscopy read</b>			<b>Local endoscopy read</b>		
	<b>Placebo N=198</b>	<b>Tofacitinib 5 mg twice daily N=198</b>	<b>Tofacitinib 10 mg twice daily N=197</b>	<b>Placebo N=198</b>	<b>Tofacitinib 5 mg twice daily N=198</b>	<b>Tofacitinib 10 mg twice daily N=197</b>
Remission <sup>a</sup>	11.1%	34.3%*	40.6%*	13.1%	39.4%*	47.7%*
Improvement of endoscopic appearance of the mucosa <sup>b</sup>	13.1%	37.4%*	45.7%*	15.7%	44.9%*	53.8%*
Normalisation of endoscopic appearance of the	4.0%	14.6%**	16.8%*	5.6%	22.2%*	29.4%*



mucosa <sup>c</sup>						
Maintenance of clinical response <sup>d</sup>	20.2%	51.5%*	61.9%*	20.7%	51.0%*	61.4%*
Remission among patients in remission at baseline <sup>a,f</sup>	10.2%	46.2%*	56.4%*	11.9%	50.8%*	65.5%*
Sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline <sup>e,f</sup>	5.1%	35.4%*	47.3%*	11.9%	47.7%*	58.2%*
Corticosteroid-free remission among patients taking corticosteroids at baseline <sup>a,g</sup>	10.9%	27.7% <sup>†</sup>	27.6% <sup>†</sup>	13.9%	32.7% <sup>†</sup>	31.0% <sup>†</sup>

\* p<0.0001; \*\*p<0.001; †p<0.05 for tofacitinib versus placebo.

N=number of patients in the analysis set.

<sup>a</sup>. Remission was defined as clinical remission (a Mayo score  $\leq$  2 with no individual subscore  $>$  1) and rectal bleeding subscore of 0.

<sup>b</sup>. 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).

<sup>c</sup>. Normalisation of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0.



<sup>d</sup>. Maintenance of clinical response was defined by a decrease from the induction study (OCTAVE Induction 1, OCTAVE Induction 2) baseline Mayo score of  $\geq 3$  points and  $\geq 30\%$ , with an accompanying decrease in the rectal bleeding subscore of  $\geq 1$  point or rectal bleeding subscore of 0 or 1. Patients were to be in clinical response at baseline of the maintenance study OCTAVE Sustain.

<sup>e</sup>. 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.

<sup>f</sup>. N=59 for placebo, N=65 for tofacitinib 5 mg twice daily, N=55 for tofacitinib 10 mg twice daily.

<sup>g</sup>. N=101 for placebo, N=101 for tofacitinib 5 mg twice daily, N=87 for tofacitinib 10 mg twice daily.

In both subgroups of patients with or without prior TNF inhibitor failure, a greater proportion of patients treated with either tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily achieved the following endpoints at week 52 of OCTAVE Sustain as compared to placebo: remission, improvement of endoscopic appearance of the mucosa, or sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline (Table 25). This treatment difference from placebo was similar between tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily in the subgroup of patients without prior TNF inhibitor failure. In the subgroup of patients with prior TNF inhibitor failure, the observed treatment difference from placebo was numerically greater for tofacitinib 10 mg twice daily than tofacitinib 5 mg twice daily by 9.7 to 16.7 percentage points across the primary and key secondary endpoints.

**Table 25: Proportion of patients meeting primary and key secondary efficacy endpoints at week 52 by TNF inhibitor therapy subgroup (OCTAVE sustain, central endoscopy read)**

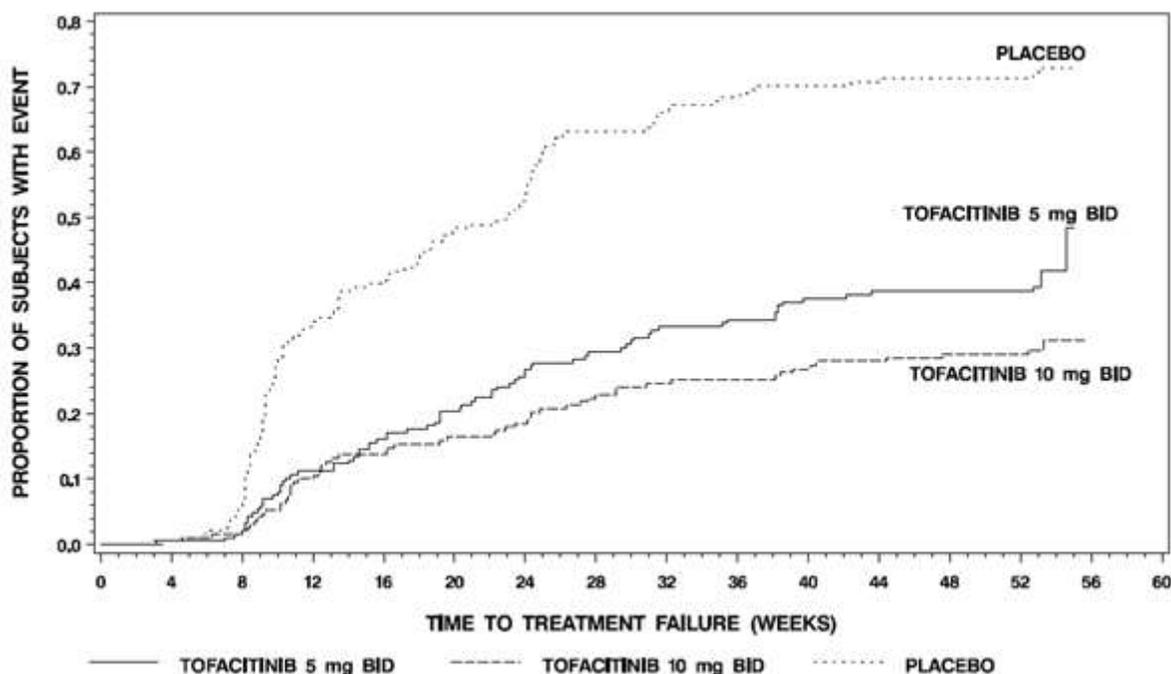
<b>Endpoint</b>	<b>Placebo N=198</b>	<b>Tofacitinib 5 mg twice daily N=198</b>	<b>Tofacitinib 10 mg twice daily N=197</b>
Remission <sup>a</sup>			
With prior TNF inhibitor failure	10/89 (11.2%)	20/83 (24.1%)	34/93 (36.6%)



Without prior TNF inhibitor failure <sup>b</sup>	12/109 (11.0%)	48/115 (41.7%)	46/104 (44.2%)
Improvement of endoscopic appearance of the mucosa <sup>c</sup>			
With prior TNF inhibitor failure	11/89 (12.4%)	25/83 (30.1%)	37/93 (39.8%)
Without prior TNF inhibitor failure <sup>b</sup>	15/109 (13.8%)	49/115 (42.6%)	53/104 (51.0%)
Sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline <sup>d</sup>			
With prior TNF inhibitor failure	1/21 (4.8%)	4/18 (22.2%)	7/18 (38.9%)
Without prior TNF inhibitor failure <sup>b</sup>	2/38 (5.3%)	19/47 (40.4%)	19/37 (51.4%)
TNF=tumour necrosis factor; N=number of patients in the analysis set.			
a. Remission was defined as clinical remission (a Mayo score $\leq$ 2 with no individual subscore > 1) <u>and</u> rectal bleeding subscore of 0.			
b. Included TNF Inhibitor naïve patients.			
c. Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).			
d. Sustained corticosteroid-free remission was defined as being in remission and not taking corticosteroids for at least 4 weeks prior to the visit at both week 24 and week 52.			

The proportion of patients in both tofacitinib groups who had treatment failure was lower compared to placebo at each time point as early as week 8, the first time point where treatment failure was assessed, as shown in Figure 2.

**Figure 2. Time to treatment failure in maintenance study OCTAVE sustain (Kaplan-Meier Curves)**



$p < 0.0001$  for tofacitinib 5 mg twice daily versus placebo.

$p < 0.0001$  for tofacitinib 10 mg twice daily versus placebo.

BID=twice daily.

Treatment failure was defined as an increase in Mayo score of  $\geq 3$  points from maintenance study baseline, accompanied by an increase in rectal bleeding subscore by  $\geq 1$  point, and an increase of endoscopic subscore of  $\geq 1$  point yielding an absolute endoscopic subscore of  $\geq 2$  after a minimum treatment of 8 weeks in the study.

#### Health-related and quality of life outcomes

Tofacitinib 10 mg twice daily demonstrated greater improvement from baseline compared to placebo in physical component summary (PCS) and mental component summary (MCS) scores, and in all 8 domains of the SF-36 in the induction studies (OCTAVE Induction 1, OCTAVE Induction 2). In the maintenance study (OCTAVE Sustain), tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily demonstrated greater maintenance of improvement compared to placebo in PCS and MCS scores, and in all 8 domains of the SF-36 at week 24 and week 52.



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

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

*Open-label extension study (OCTAVE Open)*

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

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

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

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**SUMMARY OF PRODUCT CHARACTERISTICS**  
**TOFACITINIB TABLET 5 mg (JITRIT)**

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Paediatric population

The European Medicines Agency has deferred the obligation to submit results of studies with tofacitinib in one or more subsets of the paediatric population in other rarer types of juvenile idiopathic arthritis and in ulcerative colitis (see section 4.2 for information on paediatric use).

*Polyarticular juvenile idiopathic arthritis and juvenile PsA*

The tofacitinib Phase 3 program for JIA consisted of one completed Phase 3 trial (Study JIA-I [A3921104]) and one ongoing long-term extension (LTE) (A3921145) trial. In these studies the following JIA subgroups were included: patients with either RF+ or RF- polyarthritis, extended oligoarthritis, systemic JIA with active arthritis and no current systemic symptoms (referred as pJIA dataset) and two separate subgroups of patients with juvenile PsA and enthesitis-related arthritis (ERA). However, the pJIA efficacy population only includes the subgroups with either RF+ or RF- polyarthritis or extended oligoarthritis; inconclusive results have been seen in the subgroup of patients with systemic JIA with active arthritis and no current systemic symptoms. Patients with juvenile PsA are included as separate efficacy subgroup. ERA patients are not included in the efficacy analysis.

All eligible patients in Study JIA-I received open-label tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily for 18 weeks (run-in phase); patients who achieved at least a JIA ACR30 response at the end of the open-label phase were randomised (1:1) to either active tofacitinib 5 mg film-coated tablets or tofacitinib oral solution, or placebo in the 26-week double-blind, placebo-controlled phase. Patients who did not achieve a JIA ACR30 response at the end of the open-label run-in phase or experienced a single episode of disease flare at any time were discontinued from the study. A total of 225 patients were enrolled in the open-label run-in phase. Of these, 173 (76.9%) patients were eligible to be randomised into the double-blind phase to either active tofacitinib 5 mg film-coated tablets or tofacitinib oral solution weight-based equivalent twice daily (n=88) or placebo (n=85). There were 58 (65.9%) patients in the tofacitinib group and 58 (68.2%) patients in the placebo group taking MTX during the double-blind phase, which was permitted but not required per the protocol.



There were 133 patients with pJIA [RF+ or RF- polyarthritis and extended oligoarthritis] and 15 with juvenile PsA randomised into the double-blind phase of the study and included in the efficacy analyses presented below.

### *Signs and symptoms*

A significantly smaller proportion of patients with pJIA in Study JIA-I treated with tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily flared at Week 44 compared with patients treated with placebo. A significantly greater proportion of patients with pJIA treated with tofacitinib 5 mg film-coated tablets or tofacitinib oral solution achieved JIA ACR30, 50, and 70 responses compared to patients treated with placebo at Week 44 (Table 26).

The occurrence of disease flare and JIA ACR30/50/70 results were favourable to tofacitinib 5 mg twice daily in comparison to placebo across the RF+ polyarthritis, RF- polyarthritis, extended oligoarthritis, and jPsA JIA subtypes and were consistent with those for the overall study population.

The occurrence of disease flare and JIA ACR30/50/70 results were favourable to tofacitinib 5 mg twice daily in comparison to placebo for pJIA patients who received tofacitinib 5 mg twice daily with concomitant MTX use on Day 1 [n=101 (76%)] and those who were on tofacitinib monotherapy [n=32 (24%)]. In addition, the occurrence of disease flare and JIA ACR30/50/70 results were also favourable to tofacitinib 5 mg twice daily compared to placebo for pJIA patients who had prior bDMARD experience [n=39 (29%)] and those who were bDMARD naïve [n=94 (71%)].

In Study JIA-I at Week 2 of the open-label run-in phase, the JIA ACR30 response in patients with pJIA was 45.03%.

**Table 26: Primary and secondary efficacy endpoints in patients with pJIA at Week 44\* in Study JIA-I (all p-values<0.05)**

Primary endpoint	Treatment group	Occurrence rate	Difference (%)	from
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<b>(Type I error controlled)</b>			<b>placebo (95% CI)</b>
Occurrence of disease flare	Tofacitinib 5 mg Twice Daily (N=67)	28%	-24.7 (-40.8, -8.5)
	Placebo (N=66)	53%	
<b>Secondary endpoints (Type I error controlled)</b>	<b>Treatment group</b>	<b>Response rate</b>	<b>Difference (%) from placebo (95% CI)</b>
JIA ACR30	Tofacitinib 5 mg Twice Daily (N=67)	72%	24.7 (8.50, 40.8)
	Placebo (N=66)	47%	
JIA ACR50	Tofacitinib 5 mg Twice Daily (N=67)	67%	20.2 (3.72, 36.7)
	Placebo (N=66)	47%	
JIA ACR70	Tofacitinib 5 mg Twice Daily (N=67)	55%	17.4 (0.65, 34.0)
	Placebo (N=66)	38%	
<b>Secondary endpoint (Type I error controlled)</b>	<b>Treatment group</b>	<b>LS mean (SEM)</b>	<b>Difference from placebo (95% CI)</b>
Change from Double-Blind	Tofacitinib 5 mg	-0.11 (0.04)	-0.11 (-0.22, -0.01)



Baseline in CHAQ Disability Index	Twice Daily (N=67; n=46)		
	Placebo (N=66; n=31)	0.00 (0.04)	

ACR = American College of Rheumatology; CHAQ = childhood health assessment questionnaire; CI = confidence interval; LS = least squares; n = number of patients with observations at the visit; N = total number of patients; JIA = juvenile idiopathic arthritis; SEM = standard error of the mean

\* The 26-week double-blind phase is from Week 18 through Week 44 on and after randomisation day.

The Type-I error-controlled endpoints are tested in this order: Disease Flare, JIA ACR50, JIA ACR30, JIA ACR70, CHAQ Disability Index.

In the double-blind phase, each of the components of the JIA ACR response showed greater improvement from the open-label baseline (Day 1) at Week 24, and Week 44 for patients with pJIA treated with tofacitinib oral solution dosed as 5 mg twice daily or weight-based equivalent twice daily compared with those receiving placebo in Study JIA-I.

#### *Physical function and health-related quality of life*

Changes in physical function in Study JIA-I were measured by the CHAQ Disability Index. The mean change from the double-blind baseline in CHAQ-Disability Index in patients with pJIA was significantly lower in the tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily compared to placebo at Week 44 (Table 26). The mean change from the double-blind baseline in CHAQ Disability Index results were favourable to tofacitinib 5 mg BID in comparison to placebo across the RF+ polyarthritis, RF- polyarthritis, extended oligoarthritis, and jPsA JIA subtypes and were consistent with those for the overall study population.

## **5.2 Pharmacokinetic properties**

The PK profile of tofacitinib is characterized by rapid absorption (peak plasma concentrations are reached within 0.5-1 hour), rapid elimination (half-life of ~3 hours) and dose-proportional



increases in systemic exposure. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after twice daily administration.

#### Absorption and distribution

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

After intravenous administration, the volume of distribution is 87 L. Approximately 40% of circulating tofacitinib is bound to plasma proteins. Tofacitinib binds predominantly to albumin and does not appear to bind to  $\alpha$ 1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

#### Biotransformation and elimination

Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged active substance, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. All metabolites have been observed in animal species and are predicted to have less than 10-fold potency than tofacitinib for JAK1/3 inhibition. No evidence of stereo conversion in human samples was detected. The pharmacologic activity of tofacitinib is attributed to the parent molecule. *In vitro*, tofacitinib is a substrate for MDR1, but not for breast cancer resistance protein (BCRP), OATP1B1/1B3, or OCT1/2.

#### Pharmacokinetics in patients

The enzymatic activity of CYP enzymes is reduced in RA patients due to chronic inflammation. In RA patients, the oral clearance of tofacitinib does not vary with time, indicating that treatment with tofacitinib does not normalise CYP enzyme activity.



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

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

#### Renal impairment

Subjects with mild (creatinine clearance 50-80 mL/min), moderate (creatinine clearance 30-49 mL/min), and severe (creatinine clearance < 30 mL/min) renal impairment had 37%, 43% and 123% higher AUC, respectively, compared to subjects with normal renal function. In subjects with end-stage renal disease (ESRD), contribution of dialysis to the total clearance of tofacitinib was relatively small. Following a single dose of 10 mg, mean AUC in subjects with ESRD based on concentrations measured on a non-dialysis day was approximately 40% (90% confidence intervals: 1.5-95%) higher compared to subjects with normal renal function. In clinical trials, tofacitinib was not evaluated in patients with baseline creatinine clearance values (estimated by Cockcroft-Gault equation) less than 40 mL/min.

#### Hepatic impairment

Subjects with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had 3%, and 65% higher AUC, respectively, compared to subjects with normal hepatic function. In clinical trials, tofacitinib was not evaluated in subjects with severe (Child Pugh C) hepatic impairment, or in patients screened positive for hepatitis B or C.



### Interactions

Tofacitinib is not an inhibitor or inducer of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) and is not an inhibitor of UGTs (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7). Tofacitinib is not an inhibitor of MDR1, OATP1B1/1B3, OCT2, OAT1/3, or MRP at clinically meaningful concentrations.

### Comparison of PK of prolonged-release and film-coated tablet formulations

Tofacitinib 11 mg prolonged-release tablets once daily have demonstrated PK equivalence (AUC and  $C_{max}$ ) to tofacitinib 5 mg film-coated tablets twice daily.

### Paediatric population

#### *Pharmacokinetics in paediatric patients with juvenile idiopathic arthritis*

Population PK analysis based on results from both tofacitinib 5 mg film-coated tablets twice daily and tofacitinib oral solution weight-based equivalent twice daily indicated that tofacitinib clearance and volume of distribution both decreased with decreasing body weight in JIA patients. The available data indicated that there were no clinically relevant differences in tofacitinib exposure (AUC), based on age, race, gender, patient type or baseline disease severity. The between-subject variability (% coefficient of variation) in (AUC) was estimated to be approximately 24%.

### **5.3 Preclinical safety data**

In non-clinical studies, effects were observed on the immune and hematopoietic systems that were attributed to the pharmacological properties (JAK inhibition) of tofacitinib. Secondary effects from immunosuppression, such as bacterial and viral infections and lymphoma were observed at clinically relevant doses. Lymphoma was observed in 3 of 8 adult monkeys at 6 or 3 times the clinical tofacitinib exposure level (unbound AUC in humans at a dose of 5 mg or 10 mg twice daily), and 0 of 14 juvenile monkeys at 5 or 2.5 times the clinical exposure level of 5 mg or 10 mg twice daily. Exposure in monkeys at the no observed adverse effect level (NOAEL)



for the lymphomas was approximately 1 or 0.5 times the clinical exposure level of 5 mg or 10 mg twice daily. Other findings at doses exceeding human exposures included effects on the hepatic and gastrointestinal systems.

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

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib was not carcinogenic in mice at exposures up to 38 or 19 times the clinical exposure level at 5 mg or 10 mg twice daily. Benign testicular interstitial (Leydig) cell tumours were observed in rats: benign Leydig cell tumours in rats are not associated with a risk of Leydig cell tumours in humans. Hibernomas (malignancy of brown adipose tissue) were observed in female rats at exposures greater than or equal to 83 or 41 times the clinical exposure level at 5 mg or 10 mg twice daily. Benign thymomas were observed in female rats at 187 or 94 times the clinical exposure level at 5 mg or 10 mg twice daily.

Tofacitinib was shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility (decreased pregnancy rate; decreases in the numbers of corpora lutea, implantation sites, and viable foetuses; and an increase in early resorptions), parturition, and peri/postnatal development. Tofacitinib had no effects on male fertility, sperm motility or sperm concentration. Tofacitinib was secreted in milk of lactating rats at concentrations approximately 2-fold those in serum from 1 to 8 hours post dose.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Microcrystalline Cellulose

Lactose Monohydrate

Croscarmellose Sodium

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**TOFACITINIB TABLET 5 mg (JITRIT)**

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Magnesium Stearate

Opadry white 03G580003

Ingredients of Opadry white 03G580003:- Hypromellose, Titanium Dioxide, Polyethylene Glycol and Triacetin

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

36 Months from the date of Manufacturing

### **6.4 Special precautions for storage**

Store below 30°C. Keep away from reach of children.

### **6.5 Nature and contents of container**

Alu/PVC Blister (4x15 pack)

### **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## **7. Marketing authorization holder**

Micro labs Limited

31, Race Course Road

Bangalore-560001

INDIA

## **8. Marketing authorization number(S)**

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**9. Date of first authorization/renewal of the authorization**

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**10. Date of revision of the text**

Aug 2022