SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

XELJANZ 11 mg prolonged-release tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains tofacitinib citrate, equivalent to 11 mg tofacitinib.

Excipient with known effect

Each prolonged-release tablet contains 152.23 mg of sorbitol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged-release tablet

Pink, oval tablet of approximate average dimension of 10.8 mm × 5.5 mm × 4.4 mm (length by width by thickness) with a drilled hole at one end of the tablet band and “JKI 11” printed on one side of the tablet.

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) (see section 5.1). Tofacitinib can be given as

monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see sections 4.4 and 4.5).

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 (see section 5.1).

Ankylosing spondylitis

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

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, psoriatic arthritis, and ankylosing spondylitis

The recommended dose is one 11 mg prolonged-release tablet administered once 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[a]	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.

[a] See section 5.2 for comparison of pharmacokinetics of prolonged-release and film-coated formulations.

Dose interruption and discontinuation

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 2, 3 and 4 below, recommendations for temporary dose interruption or permanent discontinuation of treatment are made according to the severity of laboratory abnormalities (see section 4.4).

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

Table 2: Low absolute lymphocyte count

Low absolute lymphocyte count (ALC) (see section 4.4)	
Laboratory value (cells/mm^3)	**Recommendation**
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, tofacitinib 11 mg prolonged-release dosing should be interrupted. When ALC is greater than 750, treatment should be resumed as clinically appropriate.
ALC less than 500	If laboratory value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in patients with an absolute neutrophil count (ANC) less than 1,000 cells/mm^3.

Table 3: Low absolute neutrophil count

Low absolute neutrophil count (ANC) (see section 4.4)	
Laboratory Value (cells/mm^3)	**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, tofacitinib 11 mg prolonged-release dosing should be interrupted. When ANC is greater than 1,000, treatment should be resumed as clinically appropriate.
ANC less than 500	If laboratory value confirmed by repeat testing within 7 days, dosing should be discontinued.

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

Table 4: Low haemoglobin value

Low haemoglobin value (Section 4.4)	
Laboratory Value (g/dL)	**Recommendation**
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) (see section 4.5) as follows:

- Tofacitinib dose should be reduced to 5 mg film-coated tablet once daily in patients receiving 11 mg prolonged-release tablet once daily.

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 4.4 for Use in patients over 65 years of age.

Hepatic impairment

Table 5: Dose adjustment for hepatic impairment

Hepatic impairment category	**Classification**	**Dose adjustment in hepatic impairment for different strength tablets**
Mild	Child Pugh A	No dose adjustment required.
Moderate	Child Pugh B	Dose should be reduced to 5 mg film-coated tablets once daily when the indicated dose in the presence of normal hepatic function is 11 mg prolonged-release tablet once daily (see section 5.2).
Severe	Child Pugh C	Tofacitinib should not be used in patients with severe hepatic impairment (see section 4.3).

Renal impairment

Table 6: Dose adjustment for renal impairment

Renal impairment Category	**Creatinine clearance**	**Dose adjustment in renal impairment for different strength tablets**
Mild	50-80 mL/min	No dose adjustment required.
Moderate	30-49 mL/min	No dose adjustment required.
Severe (including patients undergoing haemodialysis)	< 30 mL/min	Dose should be reduced to 5 mg film-coated tablet once daily when the indicated dose in the presence of normal renal function is 11 mg prolonged-release tablet once daily (see section 5.2). Patients with severe renal impairment should remain on a reduced dose even after haemodialysis (see section 5.2).

Paediatric population

The safety and efficacy of tofacitinib prolonged-release formulation in children aged 0 to less than 18 years have not been established.

No data are available.

Method of administration

Oral use.

Tofacitinib is given orally with or without food.

Tofacitinib 11 mg prolonged-release tablets must be taken whole in order to ensure the entire dose is delivered correctly. They must not be crushed, split or chewed.

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 (see section 4.4).
- Severe hepatic impairment (see section 4.2).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Tofacitinib should only be used if no suitable treatment alternatives are available in patients:
-65 years of age and older;
-patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);
-patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Use in patients 65 years of age and older

Considering the increased risk of serious infections, myocardial infarction, malignancies and all cause mortality with tofacitinib in patients 65 years of age and older, tofacitinib should only be used in these patients if no suitable treatment alternatives are available (see further details below in section 4.4 and section 5.1).

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 immunosuppressants such as

azathioprine, 6-mercaptopurine, ciclosporin 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, cerebral venous sinus thrombosis (CVST), and deep vein thrombosis (DVT), have been observed in patients taking tofacitinib (see Table 7 in section 4.8). In a randomised post-authorisation safety study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, a dose dependent increased risk for VTE was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

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 ≥2× ULN versus those with D-dimer level <2×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 ≥2× ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D-Dimer testing in this study.

In patients with cardiovascular or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events (including myocardial infarction)” and “Malignancies and lymphoproliferative disorders”) tofacitinib should only be used if no suitable treatment alternatives are available.

In patients with VTE risk factors other than MACE or malignancy risk factors, tofacitinib should be used with caution. VTE risk factors other than MACE or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.

For patients with RA with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is ≥ 2× ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib.

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

Retinal venous thrombosis

Retinal venous thrombosis (RVT) has been reported in patients treated with tofacitinib (see section 4.8). The patients should be advised to promptly seek medical care in case they experience symptoms suggestive of RVT.

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 (see section 4.8). The risk of opportunistic infections is higher in Asian geographic regions (see section 4.8). 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 (see section 4.8). In patients 65 years of age and older, tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1).

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

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) have been observed in patients receiving tofacitinib (see section 4.8).

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^3 (see section 4.2).
- 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 studies. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with tofacitinib.

At least one confirmed case of progressive multifocal leukoencephalopathy (PML) has been reported in RA patients receiving tofacitinib in the post marketing setting. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological symptoms.

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 (see sections 4.8 and 5.1). In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic

cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1).

Malignancies and lymphoproliferative disorder

Tofacitinib may affect host defences 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 malignancies particularly NMSC, lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

NMSC 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 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1). Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer (see Table 7 in section 4.8).

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 studies 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 studies although the role of JAK inhibition in these events is not known. Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis, 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.

Fractures

Fractures have been observed in patients treated with tofacitinib.

Tofacitinib should be used with caution in patients with known risk factors for fractures such as elderly patients, female patients and patients with corticosteroid use, regardless of indication and dosage.

Liver enzymes

Treatment with tofacitinib was associated with an increased incidence of liver enzyme elevation in some patients (see section 4.8 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 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^3 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^3. Lymphocytes should be monitored at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts (see section 4.2).

Neutrophils
Treatment with tofacitinib was associated with an increased incidence of neutropenia (less than 2,000 cells/mm^3) compared to placebo. It is not recommended to initiate tofacitinib treatment in patients with an ANC less than 1,000 cells/mm^3. 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 4.2).

Haemoglobin
Treatment with tofacitinib has been associated with decreases in haemoglobin levels. It is not recommended to initiate tofacitinib treatment in patients with a haemoglobin value less than 9 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 4.2).

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 hyperlipidaemia. Increases in total and LDL cholesterol associated with tofacitinib may be decreased to pretreatment levels with statin therapy.

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

Vaccinations

Prior to initiating tofacitinib, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation 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.

Gastrointestinal obstruction with a non-deformable prolonged-release formulation

Caution should be used when administering tofacitinib prolonged-release tablets to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other medicinal products utilising a non-deformable prolonged-release formulation.

Excipients contents

Tofacitinib prolonged-release tablets contain sorbitol. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

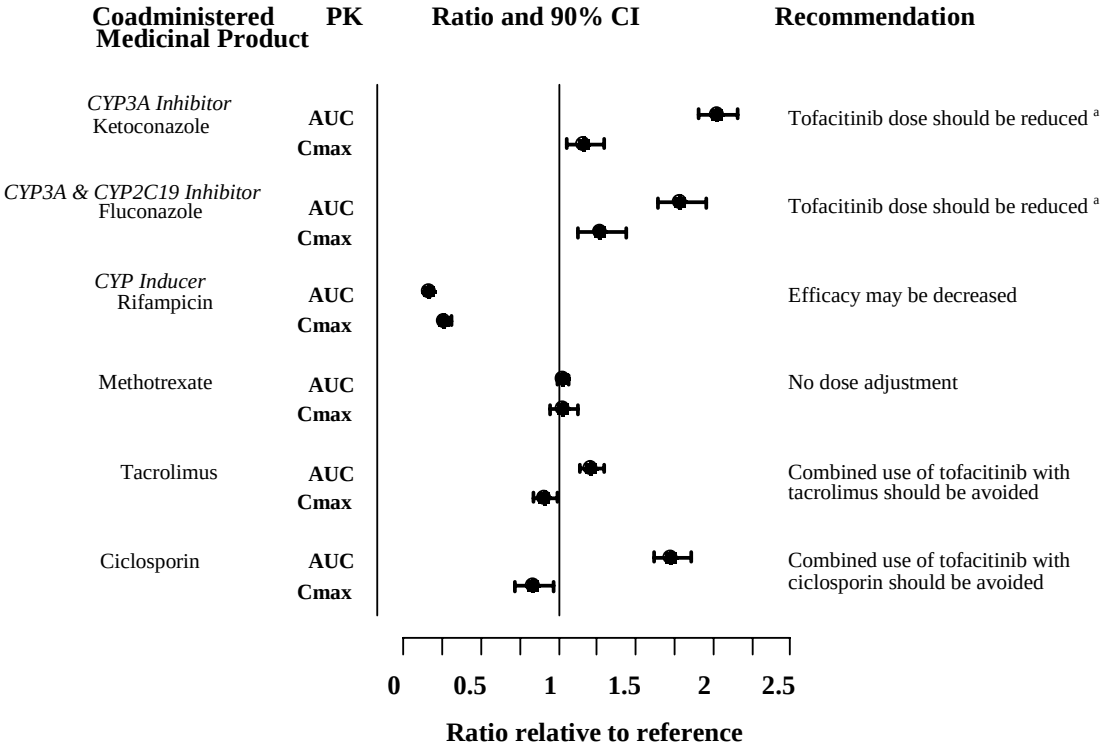
Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib

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) (see section 4.2).

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 ciclosporin (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 (see Figure 1). Coadministration of potent inducers of CYP3A4 with tofacitinib is not recommended. Coadministration with ketoconazole and fluconazole increased tofacitinib C_{max}, while tacrolimus, ciclosporin 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 (see Figure 1).

Figure 1. Impact of other medicinal products on PK of tofacitinib



Note: Reference group is administration of tofacitinib alone.

[a] Tofacitinib dose should be reduced to 5 mg (as film-coated tablet) once daily in patients receiving 11 mg (as prolonged-release tablet) once daily (see section 4.2).

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_{max} of MTX by 10% and 13%, respectively. The extent of decrease in MTX exposure does not warrant modifications to the individualised dosing of MTX.

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 (see section 5.3).

As a precautionary measure, the use of tofacitinib during pregnancy is contraindicated (see section 4.3).

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 (see section 5.3). As a precautionary measure, the use of tofacitinib during breast-feeding is contraindicated (see section 4.3).

Fertility

Formal studies of the potential effect on human fertility have not been conducted. Tofacitinib impaired female fertility but not male fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

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 (see section 4.4). In the long-term safety all exposure population, the most common serious infections reported with tofacitinib were pneumonia (1.7%), herpes zoster (0.6%), urinary tract infection (0.4%), cellulitis (0.4%), diverticulitis (0.3%), and appendicitis (0.2%). Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus infection, 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 of the double-blind, placebo or MTX controlled clinical studies were headache (3.9%), upper respiratory tract infections (3.8%), viral upper respiratory tract infection (3.3%), diarrhoea (2.9%), nausea (2.7%), and hypertension (2.2%).

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 during the first 3 months in controlled clinical studies were herpes zoster (0.19%) and pneumonia (0.15%).

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.

Tabulated list of adverse reactions

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

Table 7: Adverse reactions

System organ class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very rare <1/10,000**	**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 Bacteraemia *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal Pneumonia bacterial Cytomegalovirus infection Arthritis bacterial	Tuberculosis of central nervous system Meningitis cryptococcal Necrotizing fasciitis Encephalitis Staphylococcal bacteraemia *Mycobacterium avium* complex infection Atypical mycobacterial infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Lung cancer Non-melanoma skin cancers	Lymphoma		
Blood and lymphatic system disorders	Lymphopenia Anaemia	Leukopenia Neutropenia			
Immune system disorders					Hypersensitivity * Angioedema* Urticaria*

System organ class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare <1/10,000	Not known (cannot be estimated from the available data)
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia Dehydration			
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache	Paraesthesia			
Cardiac disorders		Myocardial infarction			
Vascular disorders	Hypertension	Venous thromboembolism**			
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea Sinus congestion			
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia				
Hepatobiliary disorders		Hepatic steatosis Hepatic enzyme increased Transaminases increased Gamma glutamyl-transferase increased	Liver function test abnormal		
Skin and subcutaneous tissue disorders	Rash Acne	Erythema Pruritus			
Musculoskeletal and connective tissue disorders	Arthralgia	Joint swelling Tendonitis	Musculoskeletal pain		
General disorders and administration site conditions	Oedema peripheral	Pyrexia Fatigue			
Investigations	Blood creatine phosphokinase 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, DVT, Retinal Venous Thrombosis, and Cerebral Venous Sinus Thrombosis

Description of selected adverse reactions

Venous thromboembolism

Rheumatoid arthritis
In a large (N=4,362), randomised post-authorisation safety study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors (see section 5.1). The majority of these events were serious and some resulted in death. The incidence rates (95% CI) for PE for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.17 (0.08-0.33), 0.50 (0.32-0.74), and 0.06 (0.01-0.17) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for PE was 2.93 (0.79-10.83) and 8.26 (2.49, 27.43) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, respectively (see section 5.1). In tofacitinib-treated patients where PE was observed, the majority (97%) had VTE risk factors.

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

Overall infections

Rheumatoid arthritis
In controlled phase 3 clinical studies, the rates of infections over 0-3 months in the 5 mg film-coated tablets 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 trials, 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 trials, among the 316 patients

treated with tofacitinib 5 mg twice daily for up to 48 weeks, the frequency of infections was 35.1%.

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 (see section 4.4).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, a dose-dependent increase in serious infections was observed with tofacitinib compared to TNF inhibitors (see section 4.4).

The incidence rates (95% CI) for serious infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 2.86 (2.41, 3.37), 3.64 (3.11, 4.23), and 2.44 (2.02, 2.92) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for serious infections was 1.17 (0.92, 1.50) and 1.48 (1.17, 1.87) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily, respectively.

Ankylosing spondylitis
In the combined Phase 2 and Phase 3 clinical trials, 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 (see section 5.1), 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).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, an increase in serious infections was observed in patients 65 years of age and older for tofacitinib 10 mg twice daily compared to TNF inhibitors and to tofacitinib 5 mg twice daily (see section 4.4). The incidence rates (95% CI) for serious infections in patients ≥65 years were 4.03 (3.02, 5.27), 5.85 (4.64,

7.30), and 3.73 (2.81, 4.85) patients with events per 100 patient-years for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors, respectively.

Compared with TNF inhibitors, the hazard ratio (HR) for serious infections in patients ≥65 years of age was 1.08 (0.74, 1.58) and 1.55 (1.10, 2.19) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, respectively.

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

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^3, or patients treated with 10 mg twice daily may have an increased risk of herpes zoster (see section 4.4).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, an increase in herpes zoster events was observed in patients treated with tofacitinib compared to TNF inhibitors. The incidence rates (95% CI) for herpes zoster for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 3.75 (3.22, 4.34), 3.94 (3.38, 4.57), and 1.18 (0.90, 1.52) patients with events per 100 patient-years, respectively.

Laboratory tests

Lymphocytes
In the controlled RA clinical studies, confirmed decreases in ALC below 500 cells/mm^3 occurred in 0.3% of patients and for ALC between 500 and 750 cells/mm^3 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^3 occurred in 1.3% of patients and for ALC between 500 and 750 cells/mm^3 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^3 were associated with an increased incidence of serious infections (see section 4.4).

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

In the 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 (see section 4.4).

Platelets
Patients in the Phase 3 controlled clinical studies (RA, PsA, AS) were required to have a platelet count $\geq$ 100,000 cells/mm^3 to be eligible for enrolment, therefore, there is no information available for patients with a platelet count < 100,000 cells/mm^3 before starting treatment with tofacitinib.

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) (study I, see section 5.1), 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, see section 5.1), 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, see section 5.1), 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 a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, ALT elevations greater than or equal to 3x ULN were observed in 6.01%, 6.54% and 3.77% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors respectively. AST elevations greater than or equal to 3x ULN were observed in 3.21%, 4.57% and 2.38% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors respectively.

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 studies 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 study, 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 a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, changes in lipid parameters from baseline through 24 months are summarised below:

- Mean LDL cholesterol increased by 13.80%, 17.04%, and 5.50% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor, respectively, at month 12. At month 24, the increase was 12.71%, 18.14%, and 3.64%, respectively,
- Mean HDL cholesterol increased by 11.71%, 13.63%, and 2.82% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor, respectively, at month 12. At month 24, the increase was 11.58%, 13.54%, and 1.42%, respectively.

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 inhibitors (see sections 4.4 and 5.1). 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 4.4 and 5.1). 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 (see sections 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, Janus-associated kinase (JAK) inhibitors; ATC code: L04AF01

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 (see section 4.2 for absolute lymphocyte count monitoring).

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 study 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 medicinal product. This patient subsequently made a robust, though delayed, humoral and cellular response to the vaccine (see section 4.4).

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 8 provides information regarding the pertinent study design and population characteristics.

Table 8: Phase 3 clinical studies 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-IR	MTX-IR	MTX-IR	TNFi-IR	MTX-naïve[a]	MTX-IR
Control	Placebo	Placebo	Placebo	Placebo	Placebo	MTX	MTX, ADA
Background treatment	None[b]	csDMARDs	MTX	MTX	MTX	None[b]	3 Parallel arms: • Tofacitinib monotherapy • Tofacitinib+ MTX • ADA+MTX
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

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)
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[c]	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 mg 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

[a.] ≤3 weekly doses (MTX-naïve).
[b.] Antimalarials were allowed.
[c.] 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 9. 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 9: Proportion (%) of patients with an ACR response

ORAL Solo: DMARD inadequate responders				
Endpoint	**Time**	**Placebo N=122**	**Tofacitinib 5 mg twice daily monotherapy N=241**	**Tofacitinib 10 mg twice daily monotherapy N=243**
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
ORAL Sync: DMARD inadequate responders				
Endpoint	**Time**	**Placebo + DMARD(s) N=158**	**Tofacitinib 5 mg twice daily + DMARD(s) N=312**	**Tofacitinib 10 mg twice daily + DMARD(s) N=315**
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**	**Tofacitinib twice daily + MTX**		**Adalimumab 40 mg QOW + MTX**
ACR20		**N=105**	**5 mg N=198**	**10 mg N=197**	**N=199**
	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 N=184**	**Tofacitinib 5 mg twice daily monotherapy N=370**	**Tofacitinib 10 mg twice daily monotherapy N=394**
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***
ORAL Strategy: MTX inadequate responders				
Endpoint	**Time**	**Tofacitinib 5 mg twice daily N=384**	**Tofacitinib 5 mg twice daily + MTX N=376**	**Adalimumab + MTX N=386**
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<0.05
**p<0.001
***p<0.0001 verses placebo (versus MTX for ORAL Start)
□p<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 10.

Table 10: Number (%) of subjects achieving DAS28-4(ESR) < 2.6 remission at months 3 and 6

	Time point	**N**	**%**
ORAL Step: TNF inhibitor inadequate responders			
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
ORAL Sync: DMARD inadequate responders			
Tofacitinib 5 mg twice daily	Month 6	312	8*
Tofacitinib 10 mg twice daily	Month 6	315	11***
Placebo	Month 6	158	3
ORAL Standard: MTX inadequate responders			
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 mg 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 11, 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 mg or 10 mg twice daily respectively, both significant versus MTX.

Table 11: Radiographic changes at months 6 and 12

	ORAL Scan: MTX inadequate responders				
	Placebo + MTX N=139 Mean (SD)[a]	**Tofacitinib 5 mg twice daily + MTX N=277 Mean (SD)[a]**	**Tofacitinib 5 mg twice daily + MTX Mean difference from placebo[b] (CI)**	**Tofacitinib 10 mg twice daily + MTX N=290 Mean (SD)[a]**	**Tofacitinib 10 mg twice daily + MTX Mean difference from placebo[b] (CI)**
mTSS[c]					
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)
	ORAL Start: MTX-naïve				
	MTX N=168 Mean (SD)[a]	**Tofacitinib 5 mg twice daily N=344 Mean (SD)[a]**	**Tofacitinib 5 mg twice daily Mean difference from MTX[d] (CI)**	**Tofacitinib 10 mg twice daily N=368 Mean (SD)[a]**	**Tofacitinib 10 mg twice daily Mean difference from MTX[d] (CI)**
mTSS[c]					
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)

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

Table 12: 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
ORAL Standard: MTX inadequate responders				
N=96		**N=185**	**N=183**	**N=188**
-0.24		-0.54***	-0.61***	-0.50***
ORAL Step: TNF inhibitor inadequate responders				
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)**	
ORAL Sync: DMARD inadequate responders				
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 mg 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 mg 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 mg 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 5 years is also provided from data 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, as well as in completed open-label,
long-term follow-up studies up to 8 years.

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). The majority (more than 90%) of tofacitinib patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively. Patients were 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.

The results for adjudicated MACE, adjudicated malignancies excluding NMSC, and selected other events are provided below.

MACE (including myocardial infarction) and venous thromboembolism (VTE)

An increase in non-fatal myocardial infarction was observed in patients treated with tofacitinib compared to TNF inhibitor. A dose-dependent increase in VTE events was observed in patients treated with tofacitinib compared to TNF inhibitor (see sections 4.4 and 4.8).

Table 13: Incidence rate and hazard ratio for MACE, myocardial infarction and venous thromboembolism

	Tofacitinib 5 mg twice daily	**Tofacitinib 10 mg twice daily[a]**	**All Tofacitinib[b]**	**TNF inhibitor (TNFi)**
MACE[c]				
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)	
Fatal MI[c]				
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)	

Non-fatal MI[c]				
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)	
VTE[d]				
IR (95% CI) per 100 PY	0.33 (0.19, 0.53)	0.70 (0.49, 0.99)	0.51 (0.38, 0.67)	0.20 (0.10, 0.37)
HR (95% CI) vs TNFi	1.66 (0.76, 3.63)	3.52 (1.74, 7.12)	2.56 (1.30, 5.05)	
PE[d]				
IR (95% CI) per 100 PY	0.17 (0.08, 0.33)	0.50 (0.32, 0.74)	0.33 (0.23, 0.46)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	2.93 (0.79, 10.83)	8.26 (2.49, 27.43)	5.53 (1.70, 18.02)	
DVT[d]				
IR (95% CI) per 100 PY	0.21 (0.11, 0.38)	0.31 (0.17, 0.51)	0.26 (0.17, 0.38)	0.14 (0.06, 0.29)
HR (95% CI) vs TNFi	1.54 (0.60, 3.97)	2.21 (0.90, 5.43)	1.87 (0.81, 4.30)	

[a] 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.
[b] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
[c] Based on events occurring on treatment or within 60 days of treatment discontinuation.
[d] Based on events occurring on treatment or within 28 days of treatment discontinuation.
Abbreviations: MACE = major adverse cardiovascular events, MI = myocardial infarction, VTE = venous thromboembolism, PE = pulmonary embolism, DVT = deep vein thrombosis, 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 ≥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 sections 4.4 and 4.8).

Malignancies

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

Table 14: Incidence rate and hazard ratio for malignancies[a]

	Tofacitinib 5 mg twice daily	**Tofacitinib 10 mg twice daily[b]**	**All Tofacitinib[c]**	**TNF inhibitor (TNFi)**
Malignancies excluding NMSC				
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)	
Lung cancer				
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)	
Lymphoma				
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)	
NMSC				
IR (95% CI) per 100 PY	0.61 (0.41, 0.86)	0.69 (0.47, 0.96)	0.64 (0.50, 0.82)	0.32 (0.18, 0.52)
HR (95% CI) vs TNFi	1.90 (1.04, 3.47)	2.16 (1.19, 3.92)	2.02 (1.17, 3.50)	

[a] For malignancies excluding NMSC, lung cancer, and lymphoma, based on events occurring on treatment or after treatment discontinuation up to the end of the study. For NMSC based on events occurring on treatment or within 28 days of treatment discontinuation.
[b] 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.
[c] 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 ≥ 65 years and current or past smoking (see section 4.4 and 4.8).

Mortality
Increased mortality was observed in patients treated with tofacitinib compared to TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies.

Table 15: Incidence rate and hazard ratio for mortality[a]

	Tofacitinib 5 mg twice daily	**Tofacitinib 10 mg twice daily[b]**	**All Tofacitinib[c]**	**TNF inhibitor (TNFi)**
Mortality (all cause)				
IR (95% CI) per 100 PY	0.50 (0.33, 0.74)	0.80 (0.57, 1.09)	0.65 (0.50, 0.82)	0.34 (0.20, 0.54)
HR (95% CI) vs TNFi	1.49 (0.81, 2.74)	2.37 (1.34, 4.18)	1.91 (1.12, 3.27)	
Fatal infections				
IR (95% CI) per 100 PY	0.08 (0.02, 0.20)	0.18 (0.08, 0.35)	0.13 (0.07, 0.22)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	1.30 (0.29, 5.79)	3.10 (0.84, 11.45)	2.17 (0.62, 7.62)	
Fatal CV events				
IR (95% CI) per 100 PY	0.25 (0.13, 0.43)	0.41 (0.25, 0.63)	0.33 (0.23, 0.46)	0.20 (0.10, 0.36)
HR (95% CI) vs TNFi	1.26 (0.55, 2.88)	2.05 (0.96, 4.39)	1.65 (0.81, 3.34)	
Fatal Malignancies				
IR (95% CI) per 100 PY	0.10 (0.03, 0.23)	0.00 (0.00, 0.08)	0.05 (0.02, 0.12)	0.02 (0.00, 0.11)
HR (95% CI) vs TNFi	4.88 (0.57, 41.74)	0 (0.00, Inf)	2.53 (0.30, 21.64)	

[a] Based on events occurring on treatment or within 28 days of treatment discontinuation.
[b] 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.
[c] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
Abbreviations: TNF = tumor necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, CV = cardiovascular, Inf = infinity

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 (≥ 3 swollen and ≥ 3 tender joints). Patients were required to have active plaque psoriasis at the screening visit. For both studies, the primary endpoints were ACR20 response rate and change from baseline in HAQ-DI at month 3.

Study PsA-I (OPAL BROADEN) evaluated 422 patients who had a previous inadequate response (due to lack of efficacy or intolerance) to a csDMARD (MTX for 92.7% of patients); 32.7% of the patients in this study had a previous inadequate response to > 1 csDMARD or 1 csDMARD and a targeted synthetic DMARD (tsDMARD). In OPAL BROADEN, previous treatment with TNF inhibitor was not allowed. All patients were required to have 1 concomitant csDMARD; 83.9% of patients received concomitant MTX, 9.5% of patients received concomitant sulfasalazine, and 5.7% of patients received concomitant leflunomide.

The median PsA disease duration was 3.8 years. At baseline, 79.9% and 56.2% of patients had enthesitis and dactylitis, respectively. Patients 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[a] (TNFi-Naïve)			**TNFi inadequate responders[b]**	
	OPAL BROADEN			**OPAL BEYOND[c]**	
Treatment group	**Placebo**	**Tofacitinib 5 mg twice daily**	**Adalimumab 40 mg SC q2W**	**Placebo**	**Tofacitinib 5 mg twice daily**
N	105	107	106	131	131
ACR20					
Month 3	33%	50%[d,*]	52%[*]	24%	50%[d,***]
Month 6	NA	59%	64%	NA	60%
Month 12	NA	68%	60%	-	-
ACR50					
Month 3	10%	28%[e,**]	33%[***]	15%	30%[e,*]
Month 6	NA	38%	42%	NA	38%
Month 12	NA	45%	41%	-	-
ACR70					
Month 3	5%	17%[e,*]	19%[*]	10%	17%
Month 6	NA	18%	30%	NA	21%
Month 12	NA	23%	29%	-	-
ΔLEI[f]					
Month 3	-0.4	-0.8	-1.1[*]	-0.5	-1.3[*]
Month 6	NA	-1.3	-1.3	NA	-1.5
Month 12	NA	-1.7	-1.6	-	-
ΔDSS[f]					
Month 3	-2.0	-3.5	-4.0	-1.9	-5.2[*]
Month 6	NA	-5.2	-5.4	NA	-6.0
Month 12	NA	-7.4	-6.1	-	-

PASI75[g]					
Month 3	15	43%[d,***]	39%[**]	14%	21%
Month 6	%	46%	55%	NA	34%
Month 12	NA	56%	56%	-	-
	NA				

[*]Nominal p≤0.05; [**] Nominal p<0.001; [***] Nominal p<0.0001 for active treatment versus placebo at month 3.
Abbreviations: BSA=body surface area; ΔLEI=change from baseline in Leeds Enthesitis Index; ΔDSS=change from baseline in Dactylitis Severity Score; ACR20/50/70=American College of Rheumatology ≥ 20%, 50%, 70% improvement; csDMARD=conventional synthetic disease-modifying antirheumatic drug; N=number of randomised and treated patients; NA=Not applicable, as data for placebo treatment is not available beyond month 3 due to placebo advanced to 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=≥ 75% improvement in PASI.

[a] Inadequate response to at least 1 csDMARD due to lack of efficacy and/or intolerability.
[b] Inadequate response to a least 1 TNFi due to lack of efficacy and/or intolerability.
[c] OPAL BEYOND had a duration of 6 months.
[d] Achieved statistical significance globally at p≤ 0.05 per the pre-specified step-down testing procedure.
[e] Achieved statistical significance within the ACR family (ACR50 and ACR70) at p≤ 0.05 per the pre-specified step-down testing procedure.
[f] For patients with Baseline score > 0.
[g] For patients with Baseline BSA ≥ 3% and PASI > 0.

Both TNF inhibitor naïve and TNF inhibitor inadequate responder tofacitinib 5 mg twice daily-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 twice daily 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 twice daily, adalimumab and placebo treated patients, respectively (tofacitinib 5 mg twice daily 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 twice daily and placebo treated patients, respectively, however tofacitinib 5 mg twice daily 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≤ 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[a] (TNFi-naïve)			TNFi inadequate responders[b]	
	OPAL BROADEN			OPAL BEYOND	
Treatment group	**Placebo**	**Tofacitinib 5 mg twice daily**	**Adalimumab 40 mg SC q2W**	**Placebo**	**Tofacitinib 5 mg twice daily**
N	104	107	106	131	129
Month 3	-0.18	-0.35[c,*]	-0.38[*]	-0.14	-0.39[c,***]
Month 6	NA	-0.45	-0.43	NA	-0.44
Month 12	NA	-0.54	-0.45	NA	NA

[*] Nominal $p \leq 0.05$; [***] Nominal $p < 0.0001$ for active treatment versus placebo at month 3.
Abbreviations: DMARD=disease-modifying antirheumatic drug; HAQ-DI=Health Assessment Questionnaire Disability Index; N=total number of patients in the statistical analysis; SC q2w=subcutaneously once every 2 weeks; TNFi=tumour necrosis factor inhibitor.
[a] Inadequate response to at least one conventional synthetic DMARD (csDMARD) due to lack of efficacy and/or intolerability.
[b] Inadequate response to a least one TNF inhibitor (TNFi) due to lack of efficacy and/or intolerability.
[c] Achieved statistical significance globally at $p \leq 0.05$ per the pre-specified step-down testing procedure.

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

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

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

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

	Placebo (N=136)	**Tofacitinib 5 mg Twice Daily (N=133)**	**Difference from Placebo (95% CI)**
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 ≥ 20% and ≥ 1 unit increase in at least 3 domains on a scale of 0 to 10, and no worsening of ≥ 20% and ≥ 1 unit in the remaining domain; ASAS40 = An improvement from Baseline ≥ 40% and ≥ 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)		
	Baseline (mean)	**Week 16 (LSM change from Baseline)**	**Baseline (mean)**	**Week 16 (LSM change from Baseline)**	**Difference from Placebo (95% CI)**
ASAS Components					
– Patient Global Assessment of Disease Activity (0-10)[a,*]	7.0	-0.9	6.9	-2.5	-1.6 (-2.07, -1.05)**
– Total spinal pain (0-10)[a,*]	6.9	-1.0	6.9	-2.6	-1.6 (-2.10, -1.14)**
– BASFI (0-10)[b,*]	5.9	-0.8	5.8	-2.0	-1.2 (-1.66, -0.80)**
– Inflammation (0-10)[c,*]	6.8	-1.0	6.6	-2.7	-1.7 (-2.18, -1.25)**
BASDAI Score[d]	6.5	-1.1	6.4	-2.6	-1.4 (-1.88, -1.00)**
BASMI[e,*]	4.4	-0.1	4.5	-0.6	-0.5 (-0.67, -0.37)**
hsCRP[f,*] (mg/dL)	1.8	-0.1	1.6	-1.1	-1.0 (-1.20, -0.72)**
ASDAScrp[g,*]	3.9	-0.4	3.8	-1.4	-1.0 (-1.16, -0.79)**

* type I error-controlled.
** p<0.0001.
[a] Measured on a numerical rating scale with 0 = not active or no pain, 10 = very active or most severe pain.
[b] Bath Ankylosing Spondylitis Functional Index measured on a numerical rating scale with 0 = easy and 10 = impossible.
[c] Inflammation is the mean of two patient-reported stiffness self-assessments in BASDAI.
[d] Bath Ankylosing Spondylitis Disease Activity Index total score.
[e] Bath Ankylosing Spondylitis Metrology Index.
[f] High sensitivity C-reactive protein.
[g] 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) compared to placebo-treated patients at Week 16.

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 juvenile idiopathic arthritis and in ulcerative colitis (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following oral administration of tofacitinib 11 mg prolonged-release tablet, peak plasma concentrations are reached at 4 hours and half-life is ~6 hours. Steady state concentrations are achieved within 48 hours with negligible accumulation after once daily administration. Steady-state AUC and C_{max} of tofacitinib for tofacitinib 11 mg prolonged-release tablet administered once daily are equivalent to those of tofacitinib 5 mg film-coated tablets administered twice daily.

Absorption and distribution

Coadministration of tofacitinib 11 mg prolonged-release tablet with a high-fat meal resulted in no changes in AUC while C_{max} was increased by 27%.

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 α1-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 radiolabelled 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 AS 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 (see section 4.2). 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 studies, tofacitinib was not evaluated in patients with baseline creatinine clearance values (estimated by Cockcroft-Gault equation) less than 40 mL/min (see section 4.2).

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 studies, tofacitinib was not evaluated in subjects with severe (Child Pugh C) hepatic impairment (see sections 4.2 and 4.4), 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.

5.3 Preclinical safety data

In non-clinical studies, effects were observed on the immune and haematopoietic 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 postdose. In studies conducted in juvenile rats and monkeys, there were no tofacitinib-related effects on bone development in males or females, at exposures similar to those achieved at approved doses in humans.

No tofacitinib-related findings were observed in juvenile animal studies that indicate a higher sensitivity of paediatric populations compared with adults. In the juvenile rat fertility study, there was no evidence of developmental toxicity, no effects on sexual maturation, and no evidence of reproductive toxicity (mating and fertility) was noted after sexual maturity. In 1-month juvenile rat and 39-week juvenile monkey studies tofacitinib-related effects on immune and haematology parameters consistent with JAK1/3 and JAK2 inhibition were observed. These effects were reversible and consistent with those also observed in adult animals at similar exposures.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

sorbitol (E420)
hydroxyethyl cellulose
copovidone
magnesium stearate

Film coat

cellulose acetate
hydroxypropyl cellulose (E463)
hypromellose (E464)
titanium dioxide (E171)
triacetin
red iron oxide (E172)

Printing ink

shellac (E904)
ammomium hydroxide (E527)
propylene glycol (E1520)
black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottles with 2 silica gel desiccants and child-resistant, polypropylene closure containing 30 or 90 prolonged-release tablets.

Aluminium foil/PVC backed aluminium foil blisters containing 7 prolonged-release tablets. Each pack contains 28 or 91 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent
CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00057/1696

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 January 2021
Date of latest renewal: 08 March 2022

10 DATE OF REVISION OF THE TEXT

05/03/2026