Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 3

Extract from the Clinical Evaluation Report for Tofacitinib citrate

Proprietary Product Name: Xeljanz

Sponsor: Pfizer Australia Pty Ltd

Date of CER:
Third round: 14 August 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

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List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACR20	20% improvement in disease activity
ACR50	50% improvement in disease activity
ACR70	70% improvement in disease activity
ACR90	90% improvement in disease activity
ACRn	absolute value of the ACR score
AE	Amount of drug eliminated in urine
AE24	Cumulative amount of drug recovered unchanged in the urine up to 24 hours postdose
AE24%	Percentage of the cumulative amount of drug recovered unchanged in the urine up to 24 hours postdose
AE	adverse event
AHD	amount of CP-690,550 in dialysate collected within the collection period
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time profile
AUC0-inf	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC0-last	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
AUC0-tau	Area under the concentration-time curve from zero to interval (tau)
bd	twice daily
BID	twice daily
BMI	body mass index
BOCF	Baseline observation carried forward

Abbreviation	Meaning
BP	blood pressure
BUN	blood urea nitrogen
B2M	beta 2 microglobulin
CCP	cyclic citrullinated peptide
CCL	chemokine ligand (C-C motif)
CDNK	cyclin-dependent kinase inhibitor
CFP	culture filtrate antigen
CI	confidence interval
Clast	last quantifiable concentration
CL/F	apparent clearance
CLHD	dialyzer clearance: CLHD=AHD/(fu • Cmid • t)
CLR	renal clearance
Cmax	maximum plasma concentration
Cmid	the corresponding mid-time CP-690,550 plasma concentration
CP-690,550	tofacitinib
CSF	colony-stimulating factor
CRCL	creatinine clearance
CRP	C-reactive protein
CTX	carboxy-terminal collagen crosslinks
CTX-II	collagen type II C-telopeptide fragments
CV	coefficient of variation
CXR	chest X-ray
CYP	cytochrome P450
D	duration of absorption (in association with a zero order absorption model)
DAE	adverse event leading to discontinuation

Abbreviation	Meaning
DAS	disease activity score
DAS28-3(CRP)	disease activity score using C-reactive protein
DAS28-4(ESR)	disease activity score erythrocyte sedimentation rate
DBP	diastolic blood pressure
DILI	drug induced liver injury
DMARD	disease modifying anti-rheumatic drugs
DNA	deoxyribose nucleic acid
E	dialyser efficiency
EBV	Epstein Barr Virus
ECG	electrocardiogram
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
EQ-5D	EuroQol EQ-5D health state profile
FACIT	Functional Assessment of Chronic Illness Therapy
FACS	fluorescence activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
FID	formulation identification
FSH	follicle-stimulating hormone
fu	fraction unbound
GCP	good clinical practice
GFR	glomerular filtration rate
GI	gastrointestinal
GM-CSF	granulocyte macrophage colony-stimulating factor

Abbreviation	Meaning
GZMA	granzyme A
GZMB	granzyme B
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCRU	Rheumatoid Arthritis Healthcare Resource Utilization Questionnaire
HDLc	high density lipoprotein cholesterol
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HPF	high-powered field
HPLC-MS/MS	high-performance liquid chromatography tandem mass spectrometry
hr	hour(s)
ICH	international conference on harmonization
IFN	interferon
IgD	immunoglobulin gamma D
IgG	immunoglobulin gamma G
IgHC	immunoglobulin heavy chain
IL	interleukin
IP	interferon gamma-induced protein
IRF	interferon regulatory factor
ISG	interferon-stimulated ubiquitin-like protein
JAK	Janus Kinase
JIA	Juvenile Idiopathic Arthritis
JSN	Joint Space Narrowing

Abbreviation	Meaning
kel	terminal phase rate constant
LDLc	low density lipoprotein cholesterol
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mPASI	modified psoriasis area and severity index
mTSS	modified Total Sharp Score
MTX	methotrexate
OPC	oral powder for constitution
PD	Pharmacodynamic
PK	Pharmacokinetic
PSUR	Periodic Safety Update Report
PR	pulse rate (vital signs)
Qb	blood flow entering the dialyzer
OC	oral contraceptive
QFT-G	QuantiFERON® – TB Gold In-Tube Test
QT	QT interval of the ECG
QTc	Corrected QT interval
QTcB	QTc (Bazett's correction)
QTcF	QTc (Fridericia's correction)
QTcP	QTc (Population correction)
RA	Rheumatoid Arthritis
RBC	red blood cell
RE	relative error
RF	Rheumatoid Factor

Abbreviation	Meaning
SAE	serious adverse event
SCID	severe combined immunodeficiency disorder
SD	single dose or standard deviation, as applicable
SE	standard error
SBP	systolic blood pressure
TB	tuberculosis
TEAE	treatment emergent adverse event
t1/2	terminal half-life
Tmax	time for Cmax
T/R	test compared to reference
UGT	uridine glucuronosyl transferase
ULN	upper limit of normal
URTI	upper respiratory tract infection
V/F	apparent volume of distribution
Vss	volume of distribution in steady state
WBC	white blood cell
WCC	White cell count
WLQ	Work Limitations Questionnaire

1. Introduction

This is a supplementary report[1] evaluating additional data submitted by the Sponsor in support of a Category 1 submission to register a New Chemical Entity: tofacitinib citrate (JAQINUS / XELJANZ) 5 mg and 10 mg tablets.

The proposed indication is:

> *JAQINUS / XELJANZ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to previous DMARD therapy. JAQINUS XELJANZ can be used alone or in combination with DMARDS, including methotrexate.*

1.1. Overseas regulatory issues

Applications have been lodged in the EU (26th October 2011), the US (21 October 2011), Canada (30th March 2012) and Switzerland (25th November 2011). These applications were all under evaluation when the initial application was lodged with the TGA.

The requested indication in the US does not include use in combination with DMARDS, including MTX. The requested indication in the EU includes combination with MTX, but does not specifically mention DMARDs in general.

The Australian dossier was based on the European (EU) MAA submitted in October 2011 but included some additional data. Subsequent to the EU submission, two studies were completed and reports of these were included in the Australian dossier. These included a non-clinical study (11GR383) and a drug-drug interaction study (A3921143). Another study (2501-010) for which a complete report had since become available was also included in the Australian dossier.

Subsequently, the application for approval of tofacitinib 5 mg in the EU has been refused by the CHMP. The issues identified by the CHMP were (extracted from the EMA Opinion of the committee for medicinal products for human use on the granting of a marketing authorisation Xeljanz [tofacitinib]):

> Efficacy:
>
> "Data from five pivotal studies has been provided to support the clinical efficacy of tofacitinib 5 mg and 10 mg for the treatment of rheumatoid arthritis in different patient populations. During the assessment, to address safety concerns, the Applicant proposed to restrict the daily dose to 5 mg BID and the indication to patients with inadequate response to at least two disease modifying antirheumatic drugs (DMARDs), including MTX (multiple DMARD-IR) and biologic DMARD-inadequate responders (Biologic DMARD-IRs). Taking together the data from these studies, the efficacy demonstration of tofacitinib is not considered fully established as generally consistent results have only been achieved for the improvements of signs and symptoms (ACR 20) and physical function (HAQ-DI). The data on the impact of disease activity (achieving a DAS28 score of <2.6) are not compelling.
>
> A beneficial effect on structural damage could not be demonstrated for the 5 mg dose in the target population. In the pivotal study (study 1044) for the investigation of effect on structural damage, the primary endpoint (mTSS) only reached statistical significance for

[1] This supplementary report was prompted when the sponsor notified the TGA of a negative opinion of the CHMP, recommending against market authorisation for tofacitinib on the grounds of safety concerns (see section 1.1, below). The sponsor also supplied additional data that had become available since the original submission to the TGA, for evaluation by the TGA prior to making a decision.

the higher (10 mg) dose and not the lower (5 mg) dose. In addition, there was concern that the statistical methods employed to handle patients who discontinued from the randomised treatment may overestimate the treatment effect.

Supportive data from another study in MTX-naïve patients, where efficacy on structural damage was shown for both tofacitinib doses, was not considered sufficient by the CHMP to overcome this failure to demonstrate efficacy on structural damage in the proposed target population due to the uncertainty as to whether the data can be extrapolated to the target population as defined by the indication above.

The CHMP therefore concluded that the clinical efficacy of tofacitinib was insufficiently established for the claimed indication and posology in the target patient population.

Safety issues:

In general, patients with rheumatoid arthritis are at a higher risk of infection and cardiovascular disease and with higher mortality rate than adults in the general population. This is likely due to both altered immunological functions (as a consequence of disease) as well as other factors, including treatments for the condition.

The tofacitinib development programme provided safety data from almost 5000 subjects, however with limited long-term follow up data. Tofacitinib is a first in class inhibitor of JAK-3 and JAK-3 is an integral component of the cytokine receptor for the cytokine family of IL4, IL7, IL9, IL15 and IL21. The non-clinical data demonstrated a highly selective effect of tofacitinib on T cell proliferation and differentiation. Together with a functional pharmacodynamic effect, decreases in NK cells, CD8+ and CD4+ cells were also observed in the non-clinical studies and these effects were not considered to be completely reversible.

In the Phase 3 development programme, there was an high incidence of serious infections and opportunistic infections. The spectrum of opportunistic infections included Pneumocystis Carinii, Cryptococcus and CMV and was considered to be indicative of impaired cell mediated immunity. In some cases the infections were associated with significant lymphopaenias. Further assessment of these adverse events was limited as lymphocyte subset data, in particular T-cell subset data was not systematically collected in the clinical development programme and therefore could not be adequately assessed.

In addition, the functional effects of tofacitinib on the immune system were not adequately characterised in the development programme and CHMP were therefore not reassured that the pharmacodynamic effect of tofacitinib in the target patient population had been adequately characterised. Given the mechanism of action of tofacitinib and the pre-clinical findings, a functional impact would be expected. Finally reversibility of pharmacodynamic effect was not considered to be adequately demonstrated.

Based on these uncertainties, the risks were not considered manageable in clinical practice. The applicant has proposed a large post-authorisation efficacy and safety study incorporating a long-term extension lymphocyte substudy with monitoring of lymphocyte subsets. Given the mechanism of action of tofacitinib, as well as the non-clinical and clinical study findings, this approach is however not deemed sufficient to overcome the shortcomings related to lack of monitoring, assessment of immune system functionality and assessment of the reversibility of pharmacodynamic effect, in the pre-authorisation development programme.

Other concerning aspects in relation to the safety profile relate to the high incidence of gastrointestinal perforation, as well as an increased risk of malignancy including EBV-related lymphoma. The incidence rate of malignancy was observed to be higher in the

long-term extension studies, with rates increasing between the second and third year of treatment. Also the potential for tofacitinib to cause drug-induced liver injury cannot be ruled out, given the observations that one patient met the criteria for Hy's law with no obvious alternative explanation. Tofacitinib also induces a dose-dependent increase in LDL-c leading to a potentially increased cardiovascular risk.

Overall, due to the identified and potential safety concerns, the safety profiles of both doses of tofacitinib (5 mg and 10 mg) were considered unacceptable and insufficiently characterised precluding the safe use of the medicine in clinical practice."

The grounds for refusal by the CHMP were:

Ground 1: The evidence for an effect of tofacitinib on prevention of structural damage progression in the proposed patient population (i.e. patients who have had an inadequate response or are intolerant to previous therapy with at least two other DMARDs including at least one biological DMARD) using the dose of 5mg bid is insufficient. The magnitude of effect in this population cannot be sufficiently quantified considering the limited data available in the proposed patient population and concerns over the possibility to extrapolate from the available data from other patient populations in the clinical trial programme. In addition, there is concern that the statistical methods employed to handle patients who discontinue from randomised treatment may overestimate the effects.

Ground 2: There are significant and unresolved concerns regarding the number of serious and opportunistic infections observed with tofacitinib in the clinical studies, which are indicative of impaired cell-mediated immunity. These risks are related to the primary pharmacology of this first in class agent. The clinical development programme has limitations as it did not adequately characterise these risks; relevant information from the toxicological program was not adequately followed up in the clinical development program leading to uncertainties in mechanistic understanding.

Ground 3: The overall safety profile and the uncertainties relating to safety are not acceptable, in particular the incidence and severity of infections, malignancies, lymphoma, gastro-intestinal perforations, hepatic enzymes elevations/drug-induced liver injury and lipids and cardiovascular risks. There are limited safety data in the proposed patient population and a lack of reassurance that the available data from other patient populations in the clinical trial programme is fully applicable. Consequently, there are uncertainties surrounding the magnitude of the risks and their management in clinical practice, which are not offset by the benefits of treatment.

In response to the CHMP the Sponsor has made the following points:

1. There continues to be an unmet medical need for RA treatments, particularly those utilising novel mechanisms targeting the inflammatory pathways involved in the pathogenesis of RA, to meet the needs of biologic treatment-refractory patients.
2. Tofacitinib, as a disease modifying antirheumatic drug (DMARD) that inhibits the signaling of several inflammatory cytokines, is efficacious at a dose of 5mg BID within the proposed population of RA patients in 3rd line therapy.
3. Tofacitinib, as a DMARD that inhibits cytokine signaling, has a similar risk profile to immunomodulatory bDMARDs. The safety profile in the proposed 3rd line population is consistent with the overall tofacitinib Phase 3 population. Furthermore, these risks are recognisable and manageable by healthcare professionals (HCPs) knowledgeable in the management of this disease.
4. The identified and potential risks of tofacitinib can be mitigated through a comprehensive risk management plan (RMP), including both routine and enhanced pharmacovigilance

(PV) activities, as well as additional risk minimisation measures (RMMs) targeting HCPs and patients before and during treatment.

2. Clinical rationale

See CER Round 1 (AusPAR Attachment 2).

3. Contents of the clinical dossier

3.1. Scope of the additional clinical dossier

The additional data comprises:

- Two clinical trials with pharmacodynamic data: Study A3921073 and Study A3921130
- One randomised controlled trial in support of efficacy.
- Two studies of immunogenicity in response to vaccination
- An update to the Integrated Summary of Safety
- The Sponsor's responses to the CHMP decision

3.2. Paediatric data

See CER Round 1 (AusPAR Attachment 2).

3.3. Good clinical practice

The studies presented in the additional data are stated to have been conducted according to GCP. The study reports are consistent with adherence to GCP.

4. Pharmacokinetics

The additional data did not include any new pharmacokinetic data.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

There were two studies with pharmacodynamic data: Study A3921073 and Study A3921130.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

There were no new data relating to mechanism of action.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Study A3921073 was a multicentre, Phase 2, randomised, double blind, parallel group pharmacodynamic study in subjects with RA. The study was conducted at six centres in the US from November 2009 to July 2011. The subjects underwent arthroscopy and serum measurements of cytokines. The study included subjects with active RA on a stable dose of MTX. There were 64 subjects screened, and 15 were assigned to tofacitinib and 14 to placebo. There were 16 (89.7%) females, three (10.3%) males, and the age range was 22 to 77 years. The study treatments were: tofacitinib 10 mg twice daily or placebo. Treatment duration was for 4 weeks. The outcome measures were: arthroscopy, serum mRNA, serum pro-inflammatory cytokine levels (interleukin [IL]-1β, IL-1α, IL-4, IL-6, IL-8, IL-10, IL-17A, interferon gamma-induced protein [IP]-10, tumor necrosis factor alpha [TNFα], IL-7, IL-21, IL-12p70, interferon [IFN]gamma, granulocyte macrophage colony-stimulating factor [GM-CSF], macrophage inflammatory protein [MIP]1α, monocyte chemotactic protein [MCP]1, soluble vascular endothelial growth factor [sVEGF], soluble vascular cell adhesion molecule [sVCAM]-1, soluble intercellular adhesion molecule [sICAM]-1, and granulocyte colony-stimulating factor [G-CSF]) matrix metaloprotease (MMP)3, MMP13, Osteocalcin, Osteopontin, Parathyroid Hormone (PTH), and Osteoprotegerin (OPG).

At Day 28 ACR20 response was reported in nine (60.0%) subjects, ACR50 in six (40.0%), and ACR70 in one (6.7%) in the tofacitinib group; but no subjects in the placebo group exhibited even ACR20 response. DAS28-3(CRP) was reported in eleven (73%) subjects in the tofacitinib group and three (21.4%) in the placebo. In synovial tissue, the only parameter that changed over the 28 days of treatment was CXCL10 mRNA. In blood, mRNA decreased for CD19+ and interferon-stimulated ubiquitin-like protein (ISG)15. Relative to placebo, during treatment with tofacitinib there were decreases in concentrations of IP10, MCP-1, and SAA; and increases in osteocalcin and OPG. There was a decrease in memory B cells from Day 1 to Day 28, which recovered on Day 29 (one day after treatment was ceased). CD4+ T cells increased with treatment and returned to below baseline by 24 hours after treatment was ceased. NK cell counts decreased by Day 28 and returned to baseline by Day 35.

5.2.2.2. Secondary pharmacodynamic effects

Study A3921130 was an open label, fixed sequence study to assess the effects of tofacitinib on the kinetics of cholesterol flux through the HDL/reverse cholesterol transport pathway in subjects with active RA. The study was conducted at nine centres (seven in the US and two in Hungary) from May to February 2012.

The study included subjects with RA, as defined by: satisfying at least four of seven criteria for the diagnosis of RA as defined by the American College of Rheumatology (ACR), have active disease at Screening (having both ≥4 tender/painful joints on motion, and ≥4 swollen joints), C-reactive protein (CRP) level >7 mg/L, and Class I, II, or III of the ACR 1991 Revised Criteria for Global Functional Status in RA. Healthy volunteers, used as a reference group, were to have no clinically relevant abnormalities and CRP <2 mg/L.

Subjects with RA were administered tofacitinib 10 mg twice daily for 6 weeks. Cholesterol metabolism and cholesterol kinetics flux was investigated using 13C2-cholesterol (infused over 22 hours) and 13C L-leucine (infused over 20 hours).

The study outcome measures were: HDL-C, LDL-C, and total cholesterol concentrations; cholesterol ester production rate (mg/kg/hr) and cholesterol ester fractional catabolic rate (%/hr); LDL-apoB production rate (mg/kg/hr) and fractional catabolic rate (%/hr); HDL-apoA1 production rate (mg/kg/hr) and fractional catabolic rate (%/hr); and cholesterol efflux rate (mg/kg/hr). The safety outcome measures were AEs, clinical laboratory abnormalities, vital signs, and physical examinations.

The study included 36 subjects with RA: 30 female, six male, with an age range of 29 to 67 years. The reference group was 33 healthy volunteers: 28 female, 5 male, with an age range of 26 to 65 years. The demographic characteristics of the study groups are summarized in the CSR.

At baseline, mean HDL-C, LDL-C, total cholesterol, and Apolipoprotein A1 concentrations were all lower in the RA group compared with the healthy reference group. After six weeks treatment with tofacitinib there were significant increases in all of these analytes and the mean concentrations were similar to those in the reference group.

At baseline, cholesterol ester catabolic rate was higher in the RA group than the healthy reference group. After 6 weeks treatment with tofacitinib, in the RA group there was a significant decrease in cholesterol ester catabolic rate in the RA group and the mean rate was similar to that in the healthy reference group. There was no significant difference or change in cholesterol efflux rate or cholesterol ester production rate. HDL-apoA1 production rate increased in the RA group with treatment. Concentrations of large and small HDL-C particles increased with treatment. Concentrations of large LDL-C particles increased with treatment. There was no significant change in VLDL-C particles. Lecithin-cholesterol acyltransferase activity increased by 8% from baseline in the RA group, p = 0.0184.

5.3. Evaluator's overall conclusions on pharmacodynamics

Study A3921073 indicated that the effects of tofacitinib on the expression of lymphocyte subsets were reversible within two week of ceasing treatment.

Study A3921130 can be interpreted as indicating that the increase in serum cholesterol observed with tofacitinib results from the reversal of an increase in cholesterol ester catabolic rate resulting from RA. The observed increase in cholesterol would therefore represent a normalisation of cholesterol concentrations rather than an increase.

6. Dosage selection for the pivotal studies

There were no new data relating to dose finding studies.

7. Clinical efficacy

7.1. Efficacy in comparison with MTX

7.1.1. Pivotal efficacy studies

7.1.1.1. Study A3921069

7.1.1.1.1. Study design, objectives, locations and dates

Study A3921069 was a multicentre, randomised, double blind, parallel group comparator controlled trial of tofacitinib 5 mg and 10 mg twice daily in comparison with MTX in [MTX-naïve] subjects with RA. The study was conducted at 152 sites in 29 countries from January 2010 to May 2012.

7.1.1.1.2. Inclusion and exclusion criteria

The inclusion criteria included:

- Patient was at least 18 years of age
- The patient must have met the ACR classification criteria for the diagnosis of RA by satisfying at least four of the seven criteria

- Evidence of at least three distinct joint erosions on posteroanterior (PA) hand and wrist or anteroposterior (AP) foot radiographs (locally-read) OR if radiographic evidence of joint erosion was not available, the patient must have had a positive IgM rheumatoid factor (RF+), OR anti-CCP+
- The patient must have had active disease at both screening and Baseline, as defined by having both:
- ≥6 tender/painful joints on motion, and
- ≥6 swollen joints.
- The patient must have had one at least of the following criteria at screening:
- ESR >28 mm/hr.
- CRP >7 mg/L.
- The patient must have met Class I, II or III of the ACR 1991 Revised Criteria for Global Functional Status in RA
- Patient had discontinued all disallowed concomitant medications for the required time prior to the first dose of study drug and was taking only those concomitant medications in doses and frequency allowed by the protocol
- No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB)

The exclusion criteria included:

- Had received more than 3 weekly doses of MTX or, if ≤3 weekly doses were received, MTX was stopped due to AE attributed to MTX
- Pregnant or currently lactating
- Blood dyscrasias, including confirmed: haemoglobin <9 g/dL or hematocrit <30%; absolute neutrophil count $<1.2\times10^9$/L; or platelet count $<100\times10^9$/L
- GFR <60 mL/min
- ALT or AST >1.5xULN
- Severe, progressive, or uncontrolled renal, hepatic, haematologic, gastrointestinal, metabolic (including clinically significant hypercholesterolemia), endocrine, pulmonary, cardiac or neurologic disease, including pleural effusions or ascites; and conditions contraindicating treatment with MTX, including presence of severe or significant renal or significant hepatic impairment
- Severe, progressive or uncontrolled chronic liver disease including fibrosis, cirrhosis, or recent or active hepatitis
- History of any other rheumatic autoimmune disease, other than Sjögren's syndrome
- History of an infected joint prosthesis at any time, with the prosthesis still in situ
- History of any lymphoproliferative disorder (LPD), such as EBV-related LPD, history of lymphoma, leukaemia, or signs and symptoms suggestive of current lymphatic disease
- History of recurrent (more than one episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex
- History of any infection requiring hospitalisation, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the 6 months prior to the first dose of study drug

- History of any infection requiring antimicrobial therapy within 2 weeks prior to the first dose of study drug
- Any prior treatment with non B cell-specific lymphocyte depleting agents/therapies (alemtuzumab, alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation). Patients who had received rituximab or other selective B lymphocyte depleting agents were eligible if they had not received such therapy for at least 1 year prior to study Baseline and had normal CD 19/20+ counts by fluorescence activated cell sorting (FACS) analysis
- Any patient who had been vaccinated with live or attenuated vaccines within 6 weeks
- Malignancy or with a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ
- Infection with HIV, hepatitis B virus or hepatitis C virus

7.1.1.1.3. Study treatments

The study treatments were:

- Tofacitinib 5 mg twice daily
- Tofacitinib 10 mg twice daily
- MTX 10 mg per week titrated up to 20 mg per week over 8 weeks depending upon tolerance

All other biologic and non-biologic DMARDs were discontinued with a washout period prior to study entry. Treatment duration was for 24 months.

7.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome measures were:

- Structure preservation as measured by mTSS at Month 6
- Signs and symptoms as measured by ACR70 at Month 6

The secondary efficacy outcome measures were:

- Structure preservation:
  - Actual and change from Baseline of mTSS at Months 12 and 24
  - Actual and change from Baseline of two individual components of mTSS: erosion and joint space narrowing (JSN) scores at Months 6, 12, and 24
  - The rate of non-progression in mTSS change from Baseline, defined as mTSS change ≤0.5
  - The rate of "no new erosions" defined as an erosion score change ≤0.5
- Signs and symptoms:
  - ACR20 and ACR50 responder rates
  - Actual and change from Baseline of the seven individual components (tender joint count, swollen joint count, patient assessment of arthritis pain, physician global assessment of arthritis, patient global assessment of arthritis, CRP, and HAQ-DI) of the ACR criteria variables
  - Actual and change from Baseline in DAS28, which included the following DAS: DAS28-3 (CRP) and DAS28-4 (ESR)
  - Incidences of DAS28-3 (CRP) ≤3.2 and DAS28-4 (ESR) ≤3.2

- Incidences of DAS28-3 (CRP) <2.6 and DAS28-4 (ESR) <2.6
- DAS28 response rates: no improvement vs improvement based on DAS28-3 (CRP) and DAS28-4 (ESR)
- ACR70 response for at least 6 months
- Durability of ACR20, ACR50, ACR70, and DAS28 response rates: defined as the proportion of patients who first achieved the response at each post-baseline visit and, of these, the proportion of patients that continued to sustain a response for the following consecutive visits

· Physical function and patient reported outcomes:

- HAQ-DI.
- Rates of clinically meaningful decrease in the HAQ-DI: decrease of at least 0.22, 0.3, or 0.5 units
- Actual and change from Baseline in the SF-36 eight domain scores and two component scores
- Actual and change from Baseline in Work Limitations Questionnaire (WLQ) four domain scores and the work loss index
- Actual and change from Baseline in the EuroQol EQ-5D
- RA Healthcare Resource Utilization (RA-HCRU) Questionnaire
- Actual and change from Baseline in the Medical Outcomes Study Sleep Scale (MOS-SS) and the sleep problem index
- FACIT Fatigue Scale.

The safety outcome measures were: AEs, vital signs, cardiovascular events, malignancies, serious infections, vital signs, laboratory safety tests and ECGs.

7.1.1.1.5. Randomisation and blinding methods

Randomisation was by an interactive web/telephone response system. Blinding was maintained by double dummy. All subjects received folic or folinic acid treatment. Subjects were randomised 2:2:1 to tofacitinib 5 mg, tofacitinib 10 mg and MTX.

7.1.1.1.6. Analysis populations

The FAS and safety populations included all patients who were randomized to the study and who received at least one dose of the randomized study drug.

7.1.1.1.7. Sample size

The sample size estimation was based on both primary efficacy outcome measures, and for tests of superiority for both the 5 mg and 10 mg dose levels in comparison with MTX. The sample size was calculated in order to detect with 90% power, at a level of significance of $p < 0.05$, for a difference in mTSS of 0.9 and SD of 2.8, and a difference in ACR70 response rate of 15%, with a MTX response rate of 20%. The result of the sample size calculation was not stated.

7.1.1.1.8. Statistical methods

Hypothesis tests were performed using an ANOVA model for mTSS, and difference in binomial proportions for ACR70 based on the FAS population. Multiplicity was addressed by using a hierarchical approach.

7.1.1.1.9. Participant flow

There were 1540 subjects screened, 958 were randomised and 952 received treatment: 371 with tofacitinib 5mg, 395 with tofacitinib 10 mg and 186 with MTX. There were 307 (82.1%) subjects in the tofacitinib 5 mg group, 328 (82.4%) in the tofacitinib 10 mg and 134 (72.0%) in the MTX still receiving treatment at Month 12.

7.1.1.1.10. Major protocol violations/deviations

Withdrawal due to major protocol deviations occurred for three subjects in the tofacitinib 5 mg group, eight in the tofacitinib 10 mg group and four in the MTX.

7.1.1.1.11. Baseline data

There were 753 (79.1%) females, 199 (20.9%) males and the age range was 18 to 83 years. The treatment groups were similar in demographic characteristics. The treatment groups were similar in previous DMARD treatment. The treatment groups were similar in baseline disease characteristics.

7.1.1.1.12. Results for the primary efficacy outcome

The change in mTSS (95% CI), relative to MTX, was -0.66 (-1.03 to -0.28) for tofacitinib 5 mg, p = 0.0006, and -0.81 (-1.18 to -0.44) for 10 mg, p <0.0001.

For ACR70, the difference (95% CI), tofacitinib – MTX, was 13.51 (7.05 to 19.97) % for 5 mg and 25.70 (18.99 to 32.40) % for 5 mg, p <0.0001.

Subgroup analysis indicated a decrease in effect for prior traditional DMARD treatment on the difference for tofacitinib 5 mg relative to MTX.

7.1.1.1.13. Results for other efficacy outcomes

- There were clinically and statistically significant in increases in rates of response for ACR20, ACR50 and ACR70 from Month 2 through to Month12 for both 5 mg and 10 mg tofacitinib relative to MTX. The improvements were reflected in all the components of the ACR.
- Durability of response appeared to be greater for tofacitinib compared to MTX. The percentage of subjects with ACR70 response sustained for at least 6 months was 16.44% for 5 mg, 24.56% for 10 mg and 5.91% for MTX.
- The rate of subjects with no progression in mTSS at 12 months was 81.16% for tofacitinib 5 mg, 86.76% for 10 mg and 64.71% for MTX, p <0.0001.
- There was an improvement in HAQ-DI relative to MTX for both tofacitinib doses for all on-treatment time-points.
- There was an improvement in DAS28-ESR relative to MTX for both tofacitinib doses for all on-treatment time-points. The proportion of subjects achieving DAS-28 (ESR) ≤3.2 at 12 months was 40.07% for tofacitinib 5 mg, 51.41% for 10 mg and 24.35% for MTX. The proportion of subjects achieving DAS-28 (ESR) <2.6 at 12 months was 19.53% for tofacitinib 5 mg, 22.64% for 10 mg and 12.87% for MTX.
- There was an improvement in DAS28-CRP relative to MTX for both tofacitinib doses for all on-treatment time-points. The proportion of subjects achieving DAS-28 (CRP) ≤3.2 at 12 months was 52.99% for tofacitinib 5 mg, 65.14% for 10 mg and 32.61% for MTX. The proportion of subjects achieving DAS-28 (CRP) <2.6 at 12 months was 36.96% for tofacitinib 5 mg, 29.62% for 10 mg and 20.65% for MTX.
- There were improvements in all the domain scores of the SF-36 relative to MTX for tofacitinib 10 mg at 12 months.
- There were no convincing differences between the treatments in MOS-SS.

- FACIT fatigue scales improved for both tofacitinib doses relative to MTX.
- EQ-5D improved in the tofacitinib group relative to MTX at Month 12.
- There were no significant differences between the groups in RA-HCRU or WLQ

7.1.2. Other efficacy studies

7.1.2.1. Study A3921129

Study A3921129 was a multicentre, randomized, double-blind, parallel group, placebo-controlled study evaluating immune response following administration of influenza and pneumococcal vaccines to RA patients receiving tofacitinib or placebo tofacitinib with and without background MTX treatment. The study was conducted at 50 centres (44 in the US and six in Poland) from September 2011 to February 2012.

The study included males and females ≥18 years of age who met the ACR classification criteria for the diagnosis of RA by satisfying at least four of the seven criteria; had active disease, as defined by having both ≥4 tender/painful joints on motion (out of 68 joints assessed), and ≥4 swollen joints (out of 66 joints assessed); and satisfied Class I, II, or III of the ACR 1991 Revised Criteria for Global Functional Status in RA. Subjects were excluded if there was evidence of active or latent or inadequately treated TB; if they had any documented influenza or pneumococcal infection within the last 3 months, received any vaccine within 1 month, or received an influenza vaccine within 6 months or a pneumococcal vaccine within 5 years.

The study treatments were:

- Tofacitinib 10 mg twice daily
- Placebo

Subjects were randomised 1:1, stratified by MTX use. Subjects continued with their stable treatment for RA: MTX, NSAIDs or corticosteroids. Intravenous or intramuscular corticosteroids, biologic response modifiers, and DMARDs other than MTX were not allowed during this study. On Day 29 all subjects received influenza vaccine (H1N1, H3N1, and B) and pneumococcal vaccine (including serotypes 1, 3, 4, 5, 6B, 7F, 9V, 14, 19A, 19F, 23F, 18C).

The outcome measures were humoral response to pneumococcal and influenza vaccination. The safety outcome measures were AEs, vital signs, clinical laboratory tests and ECGs.

A total of 275 subjects were screened, and 223 assigned to treatment: 112 to tofacitinib and 111 to placebo. There were 62 subjects in each group that were receiving background MTX. Of the treated subjects, 105 (93.8%) in the tofacitinib group and 106 (95.5%) in the placebo completed; and 102 (91.1%) in the tofacitinib group and 98 (88.3%) in the placebo were evaluable for immunogenicity. There were 171 (76.7%) females, 52 (23.3%) males, and the age range was 23 to 82 years. The treatment groups were similar in demographic characteristics. The response rate to pneumococcal vaccine was significantly decreased in the tofacitinib group relative to placebo: 45.1% in the tofacitinib group and 68.4% in the placebo, difference (95% CI) -23.3 (-36.6 to -9.6) %. Response to pneumococcal vaccine was partially modified by concomitant MTX. There was a similar response to influenza vaccine for both treatment groups 56.9% in the tofacitinib group and 62.2% in the placebo, difference (95% CI) -5.4 (-19.2 to 8.5) %. The decreased response to pneumococcal vaccine appeared to be for all 12 serotypes. There appeared to be a decreased response to influenza B and H3N2 strains but this did not reach statistical significance.

7.1.2.2. Vaccine substudy A3921024

Vaccine Substudy A3921024 was nested in Study A3921024 which was a long-term tolerability, safety and efficacy study conducted in subjects who had completed Studies A3921019, A3921025, A3921032, A3921035, A3921044, A3921045, A3921046, A3921064, A3921069,

A3921073, A3921109, A3921039, and A3921040. The study was evaluated in Round 1. The new data relate to a vaccine substudy. The substudy was conducted at 41 Centres in five countries from September 2011 to January 2012. Eligible subjects had been participating in Study A3921024 and had been receiving tofacitinib 10 mg twice daily for at least 3 months continuously.

The treatment groups were:

- Continuous tofacitinib 10 mg twice daily
- Tofacitinib withdrawn for 2 weeks then resumed either as monotherapy or on background MTX

Both groups were stratified by MTX comedication. Influenza and pneumococcal vaccines were administered on Day 8 after tofacitinib was withdrawn. The influenza vaccine was Fluzone and the pneumococcal vaccine was Pneumovax23.

The outcome measure was immunogenicity, as measured by antibody response to pneumococcal and influenza antigens.

There were 199 subjects screened and 199 assigned to treatment: 100 to continuous and 99 to interrupted. Of these subjects, 98 in the continuous and 95 in the interrupted received vaccine. There were 92 subjects in the continuous and 91 in the interrupted evaluable for immunogenicity. There were 170 (85.9%) female, 28 (14.1%) males, and the age range was 21 to 78 years.

There was no significant difference between the continuous and interrupted groups in immune response to the vaccines. Satisfactory humoral response to pneumococcal vaccine was reported for 75.0% subjects in the continuous group and 84.6% in the interrupted: treatment difference (95% CI) -9.6 (-24.0 to 4.7) %. Satisfactory humoral response to influenza vaccine was reported for 66.3% subjects in the continuous group and 63.7% in the interrupted: treatment difference (95% CI) 2.6 (-12.2 to 16.6) %.

7.2. Analyses performed across trials (pooled analyses and meta-analyses)

No pooled studies or meta-analysis of efficacy were provided in the additional data.

7.3. Evaluator's conclusions on clinical efficacy

In subjects with active RA, both tofacitinib 5 mg and 10 mg were superior to MTX, at doses of up to 20 mg weekly, for efficacy measures including joint preservation, for up to 12 months. The treatment effect was clinically and statistically significant. The statistical analysis was appropriate. The CHMP may be concerned that a survivor effect could bias the results of the statistical analysis. However, in Study A3921069 there were 346 (93.3%) treated subjects in the tofacitinib 5 mg group, 369 (93.4%) for 10 mg and 166 (89.2%) in the MTX included in the analysis of mTSS. Hence a survivor effect would be expected to cause bias in the direction of the MTX group. A survivor effect would be expected to bias in favour of MTX as subjects with inadequate response would be expected to drop out of the study. Hence the bias is in favour for the group with the higher drop-out rate. The secondary efficacy endpoints also strongly supported the primary efficacy analysis. The dose range for MTX was at the upper end of the recommended range for RA and was an appropriate comparator dose for assessing the efficacy of the tofacitinib doses.

There was a significant decrease in immune response to pneumococcal antigens during treatment with tofacitinib 10 mg twice daily. There appeared to be some recovery in immune response when tofacitinib was withdrawn at the time of pneumococcal vaccination.

The results of the sample size calculation for Study A3921069 were not provided in the study report. However, the study did find a statistically significant effect for the primary outcome, therefore this information would not influence the decision regarding approval.

8. Clinical safety

8.1. Studies providing evaluable safety data

Safety data were available from all the studies discussed in Section 5 and Section 7 above. There were no additional pivotal or non-pivotal safety studies.

8.2. Patient exposure

In Study A3921130 there were 36 subjects with RA exposed to tofacitinib 10 mg twice daily for 6 weeks.

In Study A3921073 there were 15 subjects exposed to tofacitinib 10 mg twice daily for 4 weeks.

In Study A3921069 there were 371 subjects treated with tofacitinib 5mg, and 395 with tofacitinib 10 mg. There were 307 (82.1%) subjects in the tofacitinib 5 mg group and 328 (82.4%) in the tofacitinib 10 mg still receiving treatment at Month 12.

In Study A3921129 there were 112 subjects exposed to tofacitinib 10 mg for up to 71 days.

In Vaccine Substudy A3921024 there were 99 subjects exposed to tofacitinib 10 mg twice daily continuously, and 99 subjects who had tofacitinib interrupted for 2 weeks. Treatment during the substudy was for up to 80 days.

8.3. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Pivotal studies

In Study A3921069 there were 797 TEAEs in 260 (70.1%) subjects in the tofacitinib 5 mg group, 959 in 294 (74.4%) in the tofacitinib 10 mg and 395 in 130 (69.9%) in the MTX. The incidence rate (95% CI) for TEAEs was 154.8 (137.1 to 174.8) /100 patient years for tofacitinib 5 mg, 183.1 (163.4 to 205.3) /100 patient years for tofacitinib 10 mg and 196.8 (165.7 to 233.7) /100 patient years for MTX. There was a statistically significant increased rate of nausea with MTX in comparison with both tofacitinib 5 mg and 10 mg. Although not statistically significant, for tofacitinib 5 mg reporting rates were higher for abdominal pain, weight increase, back pain, increased CK and hypertension; and for tofacitinib 10 mg herpes zoster, pharyngitis, bronchitis, increased weight, increased CK, increased GGT, elevated serum lipids, headache, rash and hypertension.

8.4.1.2. Other studies

In Study A3921130 there were 44 TEAEs reported in 19 (52.8%) subjects. The most frequently reported TEAEs were upper respiratory tract infection (seven subjects), headache (four) and urinary tract infection (three).

In Study A3921129 there were 108 TEAEs reported in 56 (50.0%) subjects in the tofacitinib group and 98 in 55 (49.5%) in the placebo. The most frequently reported TEAEs were upper respiratory tract infection, urinary tract infection, headache and diarrhoea.

In Vaccine Substudy A3921024 there were 50 TEAEs reported in 35 (35.4%) subjects in the continuous group and 95 in 49 (49.5%) subjects in the interrupted group. Immunisation reactions occurred more frequently in the interrupted group.

8.4.2. Treatment-related adverse events (adverse drug reactions)

8.4.2.1. Pivotal studies

In Study A3921069 there were 267 treatment related TEAEs in 140 (37.7%) subjects in the tofacitinib 5 mg group, 344 in 171 (43.3%) in the tofacitinib 10 mg and 171 in 84 (45.2%) in the MTX.

8.4.2.2. Other studies

In Study A3921130 there were ten treatment related TEAEs with no individual term occurring in more than two subjects.

In Study A3921129 there were 28 treatment related TEAEs reported in 19 (17.0%) subjects in the tofacitinib group and 19 in eleven (9.9%) in the placebo.

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

In Study A3921069 one subject died prior to randomization. Two subjects died after the 12 month cut-off period: one in the tofacitinib 10 mg group from colon cancer; one in the tofacitinib 5 mg group from acute myocardial infarction.

In Study A3921069 SAEs were reported in 24 (6.5%) subjects in the tofacitinib 5 mg group, 24 (6.1%) in the tofacitinib 10 mg and 13 (7.0%) in the MTX. The SAEs for tofacitinib were predominantly infections, pneumonia, including pneumonia, herpes zoster, bone tuberculosis, chronic bronchitis, Dengue fever and typhoid. There was one report of high grade B-cell lymphoma in the tofacitinib 10 mg group. One subject had avascular necrosis of both heads of femur in the tofacitinib 10 mg group.

8.4.3.2. Other studies

In Study A3921130, Study A3921129 and Vaccine Substudy A3921024 there were no deaths.

In Study A3921130 there were no SAEs.

In Study A3921129 SAEs were reported in four (3.6%) subjects in the tofacitinib group and three (2.7%) in the placebo. There was no apparent pattern to the SAEs.

In Vaccine Substudy A3921024 SAEs were reported in three (3.0%) subjects in the continuous group (cataract, squamous cell carcinoma of skin, and pharyngeal hemorrhage) and three (3.0%) in the interrupted (colitis, two reports of atrial flutter, and lymph node tuberculosis).

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

In Study A3921069 DAE occurred for 24 (6.5%) subjects in the tofacitinib 5 mg group, 31 (7.8%) in the tofacitinib 10 mg and 17 (9.1%) in the MTX. Five subjects in the tofacitinib groups discontinued because of elevated serum creatinine, two because of elevated transaminases and two because of elevated CK; compared with none for these conditions in the MTX group.

8.4.4.2. Other studies

In Study A3921130 there were no DAEs.

In Study A3921129 DAE occurred for four (3.6%) subjects in the tofacitinib group and one (0.9%) in the placebo. There was no apparent pattern to the DAEs.

In Vaccine Substudy A3921024, DAE occurred in no subjects in the continuous group and two (2.0%) in the interrupted (lymph node tuberculosis, and rash).

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

In Study A3921069 ALT >3xULN was reported in eight (2.2%) subjects in the tofacitinib 5 mg group, three (<1.0%) in the 10 mg and seven (3.8%) in the MTX. AST >3xULN was reported in four (1.1%) subjects in the tofacitinib 5 mg group, two (<1.0%) in the 10 mg and three (1.6%) in the MTX.

8.5.1.2. Other studies

In Study A3921130 there was one subject with elevation of GGT >3xULN and one subject with elevation of bilirubin >1.5xULN.

In Study A3921129, post baseline elevation in AST occurred for 22 (19.8%) subjects in the tofacitinib group and eleven (10.0%) in the placebo. Post baseline elevation in AST occurred for 13 (11.7%) subjects in the tofacitinib group and eight (7.3%) in the placebo. No patients had an ALT or AST value >3×ULN and a total bilirubin >2×ULN (potential Hy's law cases).

In Vaccine Substudy A3921024 there were no reports of elevated ALT or AST.

In the response to the EMEA the Sponsor states: "*One patient on 10 mg BID tofacitinib and MTX had possible drug-induced liver injury (DILI). She experienced asymptomatic transaminase elevations on study and both drugs were discontinued, without normalisation of the transaminases. Two to three (2-3) months later she developed jaundice in association with further increases in transaminase levels. The elevated liver tests responded to prednisolone and azathioprine, possibly consistent with autoimmune hepatitis, but DILI cannot be excluded.*" This case may correspond to one reported in the Sponsor's response to the Round 1 questions [see AusPAR Attachment 2].

8.5.2. Kidney function

8.5.2.1. Pivotal studies

In Study A3921069 acute renal failure was reported in nine (2.4%) subjects in the tofacitinib 5 mg group, six (1.5%) in the 10 mg and one (0.5%) in the MTX. An increase in serum creatinine of ≥33% was observed in three (<1.0%) subjects in the tofacitinib 5 mg group, nine (2.3%) in the 10 mg and one (<1.0%) in the MTX.

8.5.2.2. Other studies

In Study A3921130 there were no reported abnormalities in renal function.

In Study A3921129 one subject had elevated serum creatinine related to dehydration that resolved on treatment.

8.5.3. Other clinical chemistry

In Study A3921129, mean serum HDL, LDL and total cholesterol increased in the tofacitinib group relative to placebo.

8.5.4. Haematology

8.5.4.1. Pivotal studies

In Study A3921069 neutrophil counts <1000 neutrophils/mm3 were observed in one (<1.0%) subjects in the tofacitinib 5 mg group, two (<1.0%) in the 10 mg and none in the MTX. Platelet counts <100,000 platelets/ mm3 were observed in four (1.1%) subjects in the tofacitinib 5 mg group, one (<1.0%) in the 10 mg and none in the MTX.

8.5.4.2. Other studies

In Study A3921130 there were no clinically significant abnormalities in haematology parameters.

In Study A3921129, post baseline seven subjects in the tofacitinib group and four in the placebo were reported with neutropenia.

In Vaccine Substudy A3921024, at Visit 4, there were six subjects in the continuous group, and three in the interrupted with neutropenia.

8.5.5. Electrocardiograph

8.5.5.1. Pivotal studies

In Study A3921069 ECG abnormalities were not reported.

8.5.5.2. Other studies

In Study A3921130 there were no reported ECG changes.

8.5.6. Vital signs

In Study A3921130 two subjects had elevation in DBP and SBP.

8.5.7. Cardiovascular

8.5.7.1. Pivotal studies

In Study A3921069 hypertension was reported as a TEAE in 23 (6.2%) subjects in the tofacitinib 5 mg group, 30 (7.6%) in the 10 mg and four (2.2%) in the MTX. Congestive heart failure was reported in 13 (3.5%) subjects in the tofacitinib 5 mg group, 13 (3.3%) in the 10 mg and four (2.2%) in the MTX. Ischaemic heart disease was reported in twelve (3.2%) subjects in the tofacitinib 5 mg group, 23 (5.8%) in the 10 mg and three (1.6%) in the MTX. Elevation in creatinine phosphokinase was reported in nine (2.4%) subjects in the tofacitinib 5 mg group, 21 (5.3%) in the 10 mg and one (0.5%) in the MTX.

8.5.7.2. Other studies

In Study A3921129 one subject in each treatment group was reported with peripheral oedema. One subject in the placebo group had elevated CK. In Study A3921129 two subjects in the tofacitinib group were reported with an AE of hypertension.

8.5.8. Serious infections

8.5.8.1. Pivotal studies

In Study A3921069 serious infections were reported in eight subjects in the tofacitinib 5 mg group (herpes zoster, pleural infection, dengue fever, pneumonia (2), subcutaneous abscess, gastrointestinal infection, and typhoid fever), six in the 10 mg (herpes zoster, bone tuberculosis, gastroenteritis, chronic bronchitis, chronic pyelonephritis, and pneumonia) and two in the MTX (nasopharyngitis and gastroenteritis).

8.5.8.2. Other studies

The Sponsor provided an updated Integrated Summary of Safety. The Sponsor highlighted that the incidence rates of AEs of special interest (infection, malignancy and cardiovascular) did not

appear to be increasing over time. In comparing the two dose levels, although not statistically significant, there were numerically higher rates for serious infections, opportunistic infections and lymphoma with the 10 mg dose level.

In comparing the 5 mg and 10 mg dose levels, the incidence rate of opportunistic infections was higher with the 10 mg dose: incidence rate (95% CI) 0.46 (0.25 to 0.86) per 100/patient years for 5 mg compared with 0.65 (0.40 to 1.06) per 100 patient years for 10 mg.

8.5.9. Malignancy

In the Integrated Summary of Safety there appeared to be an increased risk of lymphoma compared to the background US population that was dose related. In the Integrated Summary of Safety the Sponsor estimates the overall incidence rate for lymphoma was 0.070 events/100 patient years (95% CI: 0.034, 0.148), the standardized incidence ratio for lymphoma in the tofacitinib RA program was 2.36 (95% CI: 0.95, 4.86), as compared with the Surveillance Epidemiology and End Result United States database. The incidence rate for lymphoma increased with dose: incidence rate (95% CI) 0.046 (0.006 to 0.33) per hundred patient years for 5 mg compared to 0.081 (0.020 to 0.33) per hundred patient years for 10 mg.

8.6. Post-marketing experience

No post-marketing data were provided in the additional data.

8.7. Evaluator's overall conclusions on clinical safety

The additional data did not identify any new safety issues but did provide additional material relating to previously identified safety issues.

In Study A3921069, hypertension and ischaemic heart disease were reported to a greater extent in the tofacitinib groups than in the MTX. As discussed in Section 8.4.7.1.1, hypertension was reported as a TEAE in 23 (6.2%) subjects in the tofacitinib 5 mg group, 30 (7.6%) in the 10 mg and four (2.2%) in the MTX. Ischaemic heart disease was reported in twelve (3.2%) subjects in the tofacitinib 5 mg group, 23 (5.8%) in the 10 mg and three (1.6%) in the MTX. Elevation in creatinine phosphokinase was reported in nine (2.4%) subjects in the tofacitinib 5 mg group, 21 (5.3%) in the 10 mg and one (0.5%) in the MTX.

The risk of serious infections, opportunistic infections and lymphoma appears to be increased with tofacitinib in comparison with placebo and MTX. However, this increased risk is most likely related to the mode of action (i.e. immunosuppression) and is common to DMARDs, both non-biological and biological.

9. Third round benefit-risk assessment

9.1. Third round assessment of benefits

In addition to the benefits identified in Round 1 and Round 2 [see AusPAR Attachment 2], the additional data indicated benefit for tofacitinib 5 mg and 10 mg in comparison to MTX in subjects with active RA. In subjects with active RA, both tofacitinib 5 mg and 10 mg were superior to MTX, at doses of up to 20 mg weekly, for efficacy measures including joint preservation, for up to 12 months. The treatment effect was clinically and statistically significant. The statistical analysis was appropriate. In Study A3921069 there were 346 (93.3%) treated subjects in the tofacitinib 5 mg group, 369 (93.4%) for 10 mg and 166 (89.2%) in the MTX included in the analysis of mTSS. A higher drop-out rate in the MTX group would be supportive of efficacy, and would not indicate a survivor bias in favour for tofacitinib. (Subjects with poorer outcome are more likely to drop out of a study, thus biasing in favour of the group

with the higher drop-out rate). The secondary efficacy endpoints also strongly supported the primary efficacy analysis. The dose range for MTX was at the upper end of the recommended range for RA and was an appropriate comparator dose for assessing the efficacy of the tofacitinib doses.

9.2. Third round assessment of risks

The additional data did not identify any new safety issues but did provide additional material relating to previously identified safety issues.

Study A3921073 indicated that the effects of tofacitinib on the expression of lymphocyte subsets were reversible within two week of ceasing treatment.

There was a significant decrease in immune response to pneumococcal antigens during treatment with tofacitinib 10 mg twice daily. There appeared to be some recovery in immune response when tofacitinib was withdrawn at the time of pneumococcal vaccination.

Study A3921130 can be interpreted as indicating that the increase in serum cholesterol observed with tofacitinib results from the reversal of an increase in cholesterol ester catabolic rate resulting from RA. The observed increase in cholesterol would therefore represent a normalisation of cholesterol concentrations rather than an increase.

In Study A3921069, hypertension and ischaemic heart disease were reported to a greater extent in the tofacitinib groups than in the MTX. As discussed in Section 8.4.7.1.1, hypertension was reported as a TEAE in 23 (6.2%) subjects in the tofacitinib 5 mg group, 30 (7.6%) in the 10 mg and four (2.2%) in the MTX. Ischaemic heart disease was reported in twelve (3.2%) subjects in the tofacitinib 5 mg group, 23 (5.8%) in the 10 mg and three (1.6%) in the MTX. Elevation in creatinine phosphokinase was reported in nine (2.4%) subjects in the tofacitinib 5 mg group, 21 (5.3%) in the 10 mg and one (0.5%) in the MTX. However, the pooled safety data did not indicate an overall increase in the risk of adverse cardiovascular outcomes.

The risk of serious infections, opportunistic infections and lymphoma appears to be increased with tofacitinib in comparison with placebo and MTX. However, these increased risks are most likely related to the mode of action (i.e. immunosuppression) and are common to DMARDs, both non-biological and biological. It is unclear whether tofacitinib confers greater risk for these events than either non-biological or biological DMARDs.

9.3. Comments on the response to the CHMP from the sponsor

CHMP response 1): There continues to be an unmet medical need for RA treatments, particularly those utilising novel mechanisms targeting the inflammatory pathways involved in the pathogenesis of RA, to meet the needs of biologic treatment-refractory patients.

In the opinion of the Evaluator, this argument is valid and is consistent with the data and the indication sought by the Sponsor.

CHMP response 2): Tofacitinib, as a disease modifying antirheumatic drug (DMARD) that inhibits the signaling of several inflammatory cytokines, is efficacious at a dose of 5mg BID within the proposed population of RA patients in 3rd line therapy.

In the opinion of the Evaluator, this argument is valid and is consistent with the data and the indication sought by the Sponsor. The CHMP is correct in identifying that in Study 1044 the effect on MTSS, relative to placebo was not statistically significant for the 5 mg dose level. The LS mean difference (95% CI) relative to placebo for mTSS in that study was -0.34 (-0.73 to 0.04) p=0.0792 for the 5 mg dose and -0.40 (-0.79 to -0.02) p = 0.0376 for the 10 mg dose. Although not statistically significant for the 5 mg dose, the effect size was similar to the 10 mg dose. In addition, there was efficacy for the other primary outcome measure (ACR20) for the 5 mg dose. On balance, in the interests of minimizing exposure to drug, the 5 mg dose could be justified.

In Study 1044, for the outcome mTSS there were 277 (86.3%) subjects in the 5 mg group included in the analysis 290 (90.1%) in the 10 mg and 139 (86.9%) in the placebo. Hence the drop-out rates were similar for this analysis. This does not support the statement from the CHMP: *"In addition, there was concern that the statistical methods employed to handle patients who discontinued from the randomised treatment may overestimate the treatment effect."*

Study A3921069 provides further support for the efficacy of both the 5 mg and 10 mg doses, for outcome measures including joint preservation.

CHMP response 3): Tofacitinib, as a DMARD that inhibits cytokine signalling, has a similar risk profile to immunomodulatory bDMARDs. The safety profile in the proposed 3rd line population is consistent with the overall tofacitinib Phase 3 population. Furthermore, these risks are recognisable and manageable by healthcare professionals (HCPs) knowledgeable in the management of this disease.

The safety profile of tofacitinib overlaps with bDMARDs with regard to the risks of infection (including serious and opportunistic infection) and malignancy. In Study A3921064 the rate of serious infections was higher with tofacitinib than with adalimumab. In addition to this there are safety concerns with regard to renal function, hepatic function and cardiovascular risk that are not common to bDMARDs. Although healthcare professions knowledgeable in the management of RA would be alert to the development of infection, malignancy has a lag-time in presentation, and the hepatic, renal and cardiovascular risks would be unexpected. In Australia, the primary care physician is often the first contact for such patients and they may be less likely to recognise the potential for serious and opportunistic infections.

CHMP response 4): The identified and potential risks of tofacitinib can be mitigated through a comprehensive risk management plan (RMP), including both routine and enhanced pharmacovigilance (PV) activities, as well as additional risk minimisation measures (RMMs) targeting HCPs and patients before and during treatment.

These risks could also be investigated in further comparative studies with bDMARDs. Pharmacovigilance activities may take many years longer to identify risks than RCTs. Approval of tofacitinib could expose patients to unacceptable risk in the interim.

However, the counter argument is that if tofacitinib were restricted to patients who had failed treatment with both non-biologic and biologic DMARDs (i.e. no alternative treatments were available) the risks may be acceptable.

9.4. Third round assessment of benefit-risk balance

The benefit-risk balance of Tofacitinib (CP-690,550), given the proposed usage, is favourable. The proposed usage is understood to be the patient population that has no alternative treatment available (i.e. has failed treatment with both biological and non-biological DMARDs, or where these agents are contraindicated).

10. Third round recommendation regarding authorisation

The Clinical Evaluator is unable to recommend approval of the submission with the indication as proposed:

> *JAQINUS / XELJANZ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to previous DMARD therapy. JAQINUS XELJANZ can be used alone or in combination with DMARDS, including methotrexate.*

The Clinical Evaluator is of the view that the indication above does not accurately reflect the arguments made by the Sponsor in response to the CHMP refusal of marketing approval. The

proposed indication does not sufficiently emphasize that tofacitinib is proposed by the Sponsor to be a third line agent, and that healthcare professionals knowledgeable in the management of RA would be required to recognize and manage the safety risks associated with this treatment.

The Clinical Evaluator would be able to recommend approval of the submission with the following amended indication:

> *JAQINUS / XELJANZ is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to previous therapy with both non-biological and biological DMARDS. JAQINUS XELJANZ can be used alone or in combination with DMARDS, including methotrexate. Therapy with JAQINUS XELJANZ should be initiated and monitored by a specialist rheumatologist.*

11. Clinical questions

11.1. Safety

1. Were there any treatment emergent ECG abnormalities in Study A3921069?
2. Have the safety data from Vaccine Substudy A3921024 previously been [provided for evaluation] in Round 1 or 2?
3. Has Study A3921152 reached completion and are the data available for evaluation?
4. One case of potential DILI was referred to by the Sponsor in their response to the CHMP decision. Is this the same case referred to in the response to the Round 1 questions?

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