Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tofacitinib citrate

Proprietary Product Name: Xeljanz

Sponsor: Pfizer Australia Pty Ltd

March 2015

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 AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% improvement in disease activity criteria
ACR50	ACR 50% improvement in disease activity criteria
ACR70	ARC 70% improvement in disease activity criteria
ACR90	ARC 90% improvement in disease activity criteria
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{24\,h}$	area under the curve over a 24 hour dose interval
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time of intake until infinity
ASA	Australian Specific Annex
bd	twice daily
CER	Clinical evaluation report
CI	confidence interval
CK	creatine kinase
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMI	Consumer Medicine Information
CSR	Clinical study report
CV	cardiovascular
DMARD	disease modifying antirheumatic drug

Abbreviation	Meaning
bDMARD	biological DMARD
tDMARD	traditional DMARD
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
EU	European Union
FDA	Food and Drug Administration (US)
GFR	glomerular filtration rate
h	hour/s
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCRU	Rheumatoid Arthritis Healthcare Resource Utilization Questionnaire
HDL-C	high density lipoprotein-cholesterol
HR	heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFN	interferon
IFNα	interferon alfa
IgM	immunoglobulin
ITT	intent to treat
IU	International units
IV	intravenous/ly
JAK	Janus Kinase
JIA	Juvenile Idiopathic Arthritis
L	litre

Abbreviation	Meaning
LDL-C	low density lipoprotein-cholesterol
LS	least squares
MedDRA	medical dictionary for regulatory activities
mTSS	modified total Sharp score
MTX	methotrexate
NOAEL	no observed adverse effect level
PD	Pharmacodynamics
PI	Product Information
PK	PK/s
PP	per protocol
PPK	population PK/s
QT	QT interval of the ECG. The QT interval is the portion of an electrocardiogram between the onset of the Q wave and the end of the T wave, representing the total time for ventricular depolarization and repolarization. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias such as torsade de pointes and sudden death.
QTc	Corrected QT interval. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval QTc is often calculated.
QTcB	QTc (Bazett's correction)
QTcF	QTc (Fridericia's correction)
QTcP	QTc (Population correction)
RA	Rheumatoid arthritis
RMP	Risk Management Plan
RNA	ribonucleic acid
SAE	serious adverse event
SD	standard deviation

Abbreviation	Meaning
SE	standard error
STAT	signal transducer and activator of transcription
$t_{½}$	half life
TEAE	treatment emergent adverse event
TNFα	Tumour Necrosis Factor alfa
T_{max}	time to reach the maximum plasma concentration
ULN	upper limit of normal
V/F	apparent volume of distribution
Vss	volume of distribution at steady state
WBC	white blood cell

Definitions

Rheumatoid arthritis signs and symptoms assessments used in clinical trials of tofacitinib

The following definitions are taken from the sponsor's clinical overview:

- **ACR20, ACR50, ACR70**

The American College of Rheumatology's ACR20 criteria for assessing response to treatment and improvement in RA, are defined as at least a 20% improvement in tender and swollen joint counts and at least a 20% improvement in 3 of the 5 remaining ACR-core set measures: patient and physician global assessments, pain, disability, and an acute-phase reactant. Similarly, ACR50, and 70 are calculated with the respective percent improvement. The acute-phase reactant used in this program for calculation of ACR responses was the C-reactive protein (CRP).

- **Disease Activity Score (DAS)**

DAS28 assessments are composite measures of disease activity that have utility in the emerging practice of using structured patient management paradigms, which employ achievement of specific disease activity targets to optimise treatment and minimise joint damage and physical disability. Both disease activity score defined using 28 joint counts and erythrocyte sedimentation rate (DAS28-4(ESR)) and DAS28-3(CRP) are commonly used, with frequently utilised disease activity score targets of < 2.6 and ≤ 3.2. Components of DAS28-4(ESR) include tender/painful joint (28), swollen joint count (28), ESR as the acute phase reactant, and the Patient Global Assessment of Arthritis. Components of DAS28-3(CRP) include tender/painful joint (28), swollen joint count (28), and CRP as the acute phase reactant.

Results are summarised for the proportion of patients achieving DAS28-4(ESR) < 2.6 (primary) and 3.2, the proportion of patients achieving DAS28-3(CRP) < 2.6 and 3.2,

proportion of patients achieving an improvement of ≥ 1.2 in DAS28-4(ESR) and DAS28-3(CRP) from baseline, and the mean changes from baseline in the DAS28-4(ESR).

· **Progression of Structural Damage Assessment (Structure Preservation)**

Radiographs of hands and feet were performed at Baseline and at various timepoints in Study A3921044. Scoring of all radiographs was done by two separate central assessors, blinded to patient randomisation sequence and visit/time of radiograph acquisition. The assessors scored the radiographs using the standardised, validated van der Heijde modified Sharp score; the two readers' grades for each patient were averaged and this composite score was compared by timepoint to determine radiographic progression. Study A3921044 is ongoing and only data through Month 12 were analysed and reported here.

· **Physical Function Assessment**

Health Assessment Questionnaire – Disability Index (HAQ-DI): The HAQ-DI assesses the degree of difficulty a patient has experienced during the previous week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities.

· **Patient Reported Outcomes**

Measures of patient reported outcomes include the SF-36 Health Survey, Medical Outcomes Study (MOS) Sleep Scale, Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Scale, EuroQol EQ-5D Health State Profile, RA Healthcare Resource Utilization Questionnaire (RA-HCRU), and the Work Limitations Questionnaire (WLQ).

· **Durability of Efficacy Response**

Durability of ACR20, ACR50, ACR70 and DAS28 response rates was assessed in studies >6 months in duration (Studies A3921044, A3921046, A3921064) as the proportion of patients who first achieved the response at each post baseline visit (e.g., at Month 1) and, of these, the proportion of patients who sustained the level of response for the subsequent consecutive visits (e.g., Month 3 to Month 12, and Month 3 to Month 24). Durability of response was also evaluated with data from Studies A3921024 and A3921041 and was assessed from the percent of patients with ACR20, ACR50, and ACR70 responses, mean HAQ-DI, and mean DAS28-4(ESR) at 1, 2, 3 months, and every 3 months thereafter.

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Rejected (initial) Approved (final)
Date of initial decision:	14 May 2014
Date of final decision:	13 January 2015
Active ingredient:	Tofacitinib (as citrate)
Product name:	Xeljanz
Sponsor's name and address:	Pfizer Australia Pty Ltd 38-42 Wharf Rd West Ryde NSW 2114
Dose form:	Film coated tablet
Strength:	5 mg
Container:	Aluminium/PVC-backed aluminium blister, and HDPE bottle
Pack sizes:	14 or 56 tablets (blister), 60 or 180 tablets (bottle)
Approved therapeutic use:	*Xeljanz is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. Xeljanz can be used alone or in combination with nonbiological DMARDs, including methotrexate.* *Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*
Route of administration:	Oral
Dosage:	Xeljanz may be used as monotherapy or in combination with methotrexate or other nonbiological DMARDs. The recommended dosage is 5 mg administered twice daily. [see approved Product Information for full *Dosage and Administration*]
ARTG numbers:	196987, 233439

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register tablets containing 5 mg or 10 mg tofacitinib (as citrate), under the trade names Jaqinus and Xeljanz, for the following indication:

> *the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to previous DMARD[1] therapy. Xeljanz/Jaqinus can be used alone or in combination with DMARDS, including methotrexate.*

The part of the application to register the 10 mg strength was withdrawn by the sponsor following receipt of the Third round clinical evaluation report (CER) and the Delegate's initial Overview (see below). The sponsor also withdrew the part of the application to register the trade name Jaqinus.

Tofacitinib is an inhibitor of the Janus kinase (JAK) family of kinases. In the mammalian immune system, JAK1, JAK2, and tyrosine kinase 2 (TyK2) are ubiquitously expressed, whereas JAK3 expression is restricted to haematopoietic cells. The proposed treatment of rheumatoid arthritis (RA, in which lymphocyte activation and proliferation play a pathogenic role) by tofacitinib is based on tofacitinib's broad effect of JAK inhibition on multiple cytokine pathways.

Rheumatoid arthritis is a chronic, systemic, inflammatory disorder of unknown aetiology that primarily involves joints, which affects approximately 1% of Australians. The prevalence of RA increases with age, and in Australia 9% of persons in the 65-74 year age group and 6% of persons aged 75 years and over reported having the condition, compared with 2% of people aged less than 64 years. The arthritis is symmetrical and may be remitting, but, if uncontrolled, may lead to destruction of joints due to erosion of cartilage and bone which leads to deformity and loss of function. Extra-articular manifestations occur in up to 40% of patients affecting a wide range of systems including the kidneys, eyes, the pleuropericardium and skin. Those with RA are also at increased risk of infections, which may be due to a combination of the underlying disease and any immune-based therapies. Current therapies aim to control the inflammatory process, and include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease modifying antirheumatic drugs (DMARDs) which may be non-biological (such as methotrexate; MTX) or biological. The latter includes agents which block the inflammatory process either by targeting cytokines (such as tumour necrosis factor alfa (TNFα) with the inhibitors infliximab or adalimumab), cytokine receptors (such as with the interleukin-1 (IL-1) receptor blocker, anakinra and IL-6 receptor antagonist, tocilizumab), by depleting CD-20 B cells (using rituximab) or by blocking up-regulation of the inflammatory response (for example by the T cell stimulation blocker, abatacept).

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 5 February 2015.

At the time the TGA considered this application, a similar application had been approved in Switzerland (July 2013), Japan (Mach 2013) and the USA (November 2012) and was under consideration in Canada.

The European Medicines Agency (EMA) refused market authorisation for tofacitinib after a series of modifications to the proposed indications and a review. The final negative opinion was given on 25 July 2013, for the indication: *Tofacitinib, in combination with Methotrexate (MTX), is indicated for treatment of moderate to severe rheumatoid arthritis in adult patients who have had an inadequate response or are intolerant to previous therapy with at least one biological DMARD. Tofacitinib can be given as monotherapy in case of*

[1] disease modifying antirheumatic drug

intolerance to MTX or where continued treatment with MTX is inappropriate. Tofacitinib has been shown to improve physical function.[2]

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

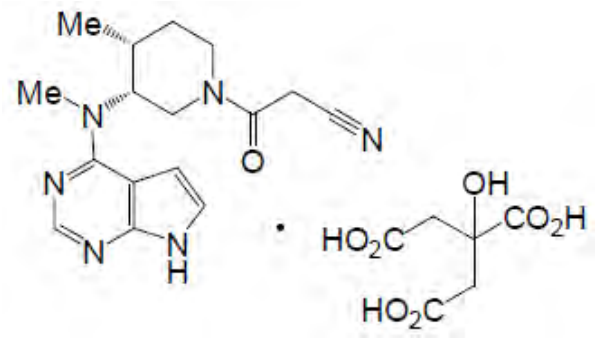
Introduction

The sponsor proposes to register film coated tablets containing 5 mg and 10 mg[3] tofacitinib citrate packed in Al/Al blister packs and HDPE bottles with child resistant closure. 14 and 56 tablets (blisters) and 60 and 180 tablets (bottles) are proposed.

Drug substance (active ingredient)

The drug substance, tofacitinib citrate, has the following structure:

Figure 1: Structure of tofacitinib citrate



Two chiral centres are present (absolute configuration R, R).

Tofacitinib citrate is manufactured by chemical synthesis. It is prepared as a crystalline powder and exhibits polymorphism. Only one crystalline form is reported. The drug substance is freely soluble in water and stated to be Biopharmaceutics Classification System (BCS) class 3.

The drug substance specification includes tests and limits for eight identified related substances. Limits for impurities that exceed the relevant International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) qualification threshold were toxicologically qualified.

[2] For full details of the EMA considerations of the application in the EU, including divergent views of 14 members of the CHMP, see EMA/CHMP/425279/2013 Committee for Medicinal Products for Human Use (CHMP). Assessment report. Xeljanz tofacitinib. Procedure No. EMEA/H/C/002542/0000 25 July 2013. [European Public Assessment Report (EPAR) for tofacitinib]

[3] The part of the application to register the 10 mg strength was withdrawn by the sponsor following receipt of the Third round clinical evaluation and Delegate's initial Overview.

Drug product

The proposed products are immediate-release film coated tablets. The manufacturing process is conventional. With the exception of the proposed coating system, the tablet formulations are direct scales.

Excipients are conventional. Tablets are distinguished by colour, size and debossing ('JKI 5' or 'JKI 10').

Assay limits comply with Therapeutic Goods Order 78.

The stability data provided supports a shelf life of 2 years when stored below 30°C in the proposed packaging.

Biopharmaceutics

Four biopharmaceutic studies have been provided.

Study A3921075 examined bioequivalence of the proposed commercial formulation (1 x 10 mg tablet) and the Phase III (2 x 5 mg tablets) and Phase IIb (2 x 5 mg tablets) formulations. The 90% confidence interval (CI) for the $\log_n$-transformed maximum concentration (Cmax) and area under the concentration-time curve (AUC) were within 80.0-125.0% for each of the compared 10 mg doses as required to conclude bioequivalence.

Study A3921077 examined the absolute bioavailability of the commercial formulation (1 x 10 mg tablet). Oral bioavailability was determined to be 74%.

Study A3921076 determined the effect of food on the 10 mg commercial tablet. Median Tmax increased from 0.5 h under fasted condition to 2 h under fed condition. Mean half life (t½) values were similar (approximately 3.1 h) between the two treatments (fasted and fed). Under fed conditions, mean $AUC_{0-\infty}$ increased by about 6% while mean Cmax decreased by 32%. The 90% CIs for the ratio of $AUC_{0-\infty}$ were within the range 80.0-125.0% while those of Cmax were outside this interval.

Study A3921005 examined the relative bioavailability of the Phase IIA formulations (2 x 5 mg tablets and 2 x 20 mg tablets) and an oral solution formulation (50 mg oral powder for constitution).

A formal justification for not submitting bioequivalence data for the proposed 5 mg tablet was not provided; however the sponsor provided data addressing the requirements of section 4 of Appendix 15 of the *Australian Regulatory Guidelines for Prescription Medicines* (ARGPM) that is acceptable from a pharmaceutical chemistry perspective.

Advisory committee considerations

The application was considered at the 149th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) on 21 January 2013. The subcommittee endorsed the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic aspects of the submission.

Quality summary and conclusions

The sponsor has provided satisfactory responses to the issues raised by the chemistry and quality (Module 3) evaluator. Registration is recommended with respect to chemistry, quality control and biopharmaceutic aspects.

III. Nonclinical findings

Introduction

The general quality of the submitted studies was high. Pivotal repeat dose toxicity studies, and definitive genotoxicity and reproductive toxicity studies were conducted under good laboratory practice (GLP) conditions. Studies not performed under GLP were adequately documented. No studies were submitted on placental transfer or the safety of tofacitinib when administered concomitantly with other drugs (such as MTX or other non-biologic DMARDs).

Tofacitinib was administered as the citrate salt in rat, mouse, rabbit, and monkey studies, reproductive studies, juvenile toxicity studies, phototoxicity studies, local tolerance studies, and in vitro and in vivo genotoxicity studies. The hydrochloride salt and free base forms were used in some in vivo and in vitro efficacy studies. All dose levels in the nonclinical report are expressed as mg of base drug per kg of body weight per day. Tofacitinib was administered to animals primarily by the oral route, which is the intended route of administration to humans.

Pharmacology

Primary pharmacology

Rationale and mechanism of action

Rheumatoid arthritis is an autoimmune disease characterised by systemic and synovial inflammation, leading to loss of function, impaired quality of life, joint destruction and excess mortality. The pathologic inflammation is accompanied by, and in part driven by, elevated levels of pro-inflammatory cytokines.

Tofacitinib is an inhibitor of the JAK family of kinases. In the mammalian immune system, JAK1, JAK2, and TyK2 are ubiquitously expressed, whereas JAK3 expression is restricted to haematopoietic cells (Yamaoka et al., 2004[4]; Aaronson et al., 2002[5]). JAK1 knockout mice display perinatal lethality (thought to be related to defective neural function, and defective lymphoid development; Rodig et al., 1998[6]), and defective innate immune responses to viruses and bacteria because of the absence of interferon (IFN) signalling (Durbin et al., 1996[7]; Meraz et al., 1996[8]). JAK2 knockout mice have embryonic lethality due to a lack of erythropoiesis (Parganas et al., 1998[9]; Neubauer et al 1998[10]). Cell lines deficient in Jak2 or Tyk2 showed no effect on granulocyte colony stimulating factor (G-CSF) dependent activation of signal transducer and activator of transcription (STAT) (Shimoda et al., 1997[11]), and cell lines deficient in Tyk2 fail to respond to IFN alfa or beta (Müller et al.,

[4] Yamaoka K, Saharinen P, Pesu M, Holt VE, III, Silvennoinen O, O'Shea JJ. The Janus kinases (Jaks). Genome Biol 2004; 5:253
[5] Aaronson DS, Horvath CM. A road map for those who don't know JAK-STAT. Science 2002; 296:1653–5
[6] Rodig SJ, Meraz MA, White JM, et al. Disruption of the Jak1 gene demonstrates obligatory and nonredundant roles of the Jaks in cytokine-induced biologic responses. Cell. 1998; 93:373-383
[7] Durbin JE, Hackenmiller R, Simon MC, Levy DE. Targeted disruption of the mouse Stat1 gene results in compromised innate immunity to viral disease. Cell. 1996; 85:443-450
[8] Meraz MA, White JM, Sheehan KCOMPARED WITH, et al. Targeted disruption of the Stat1 gene in mice reveals unexpected physiologic specificity in the JAK-STAT signaling pathway. Cell. 1996;84:431-442
[9] Parganas E, Wang D, Stravopodis D, et al. Jak2 is essential for signaling through a variety of cytokine receptors. Cell. 1998;93:385-395
[10] Neubauer H, Cumano A, Muller M, Wu H, Huffstadt U, Pfeffer K. Jak2 deficiency defines an essential developmental checkpoint in definitive hematopoiesis. Cell. 1998; 93:397-409
[11] Shimoda K, Feng J, Murakami H, et al. Jak1 plays an essential role for receptor phosphorylation and Stat activation in response to granulocyte colony-stimulating factor. Blood. 1997; 90:597-604

1993[12]; Watling et al., 1993[13]; Velasquez et al., 1992[14]). TyK2 knockout mice are viable, with lymphocyte development and proliferation not affected, but with impaired signalling by cytokines that are important for host defence (Ghoreschi et al., 2009[15]). JAK3 knockout mice display severe immunodeficiency, with T and B cell lymphopenia (Nosaka et al., 1995[16]; Park et al., 1995[17]) and dysregulated myelopoiesis (Grossman et al., 1999[18]). Autosomal recessive JAK3 deficiency in humans results in a form of severe combined immunodeficiency disease (SCID) that is characterised by lack of circulating T cells and natural killer (NK) cells, but a normal number of B cells (Notarangelo et al., 2000[19]).

The proposed treatment of RA (in which lymphocyte activation and proliferation play a pathogenic role) by tofacitinib is based on tofacitinib's broad effect of JAK inhibition on multiple cytokine pathways.

Efficacy

Tofacitinib inhibited the JAK kinase family in the nanomolar (nM) range, with functional specificity for JAK1 and JAK1/3 over JAK2 in cell assays. Blockade of JAK1/3 signalling occurs through the common gamma chain family of cytokines including interleukin (IL)-2, -4, -7, -9, -15, and 21.

In kinase assays, tofacitinib inhibited JAK1 (50% inhibitory concentration, IC_{50}, 3.2 nM), JAK2 (IC_{50} 4.1 nM), JAK3 (IC_{50} 1.6 nM), and, to a lesser extent, tyrosine kinase 2 (IC_{50} 34 nM). It inhibited IL-2 driven cell proliferation (IC_{50} 11 nM), IFN gamma production in human peripheral blood mononuclear cells (PBMC; IC_{50} 26 nM) and whole blood (IC_{50} 34 nM), and STAT5 phosphorylation in CD3+ T lymphocytes (IC_{50} 28 nM), all mediated by JAK3 and JAK1.

Tofacitinib also inhibited IL-4, IL-7, IL-15, IL-21 dependent STAT phosphorylation in T lymphocytes (JAK1/3 mediated), with IC_{50}s of 25-56 nM, which were lower than the IC_{50}s for inhibition of cellular activities mediated by heterodimeric receptors including JAK2. In whole blood, γ-common chain cytokine dependent activation (driven by JAK1/3) was inhibited by tofacitinib, in a functionally selective manner over granulocyte/macrophage (GM)-CSF dependent (JAK2-driven) activation of the pathway. When tofacitinib was tested in a kinase selectivity panel against approximately 80 distinct kinases, the IC_{50} for JAK3 was < 4 nM, and the measured IC_{50}s were ≥ 1 μM for all the rest. Using mouse whole blood ex vivo, tofacitinib inhibited IL‑15 (JAK1/3, 50% effective concentration (EC_{50}) 273 nM), IL-6 (JAK1/2, EC_{50} 470 nM), and GM-CSF (JAK2, EC_{50} 6656 nM),-driven STAT phosphorylation.

In vivo, an antirheumatic effect of tofacitinib was demonstrated in the mouse collagen induced arthritis (CIA) model and the rat adjuvant induced arthritis (AIA) model.

[12] Müller M, Briscoe J, Laxton C, et al. The protein tyrosine kinase JAK1 complements defects in interferon-α/β and -γ signal transduction. Nature. 1993; 366:129-135
[13] Watling D, Guschin D, Muller M, et al. Complementation by the protein tyrosine kinase JAK2 of a mutant cell line defective in interferon-gamma signal transduction. Nature. 1993; 366:166-170
[14] Velazquez L, Fellous M, Stark GR, Pellegrini S. A protein tyrosine kinase in the interferon alpha/beta signaling pathway. Cell. 1992; 70:313-322
[15] Ghoreschi, K., Laurence, A. and O'Shea, J. J. (2009), Janus kinases in immune cell signaling. Immunological Reviews, 228: 273–287
[16] Nosaka T, van Deursen JM, Tripp RA, et al. Defective lymphoid development in mice lacking Jak3. Science. 1995; 270:800-802
[17] Park SY, Saijo K, Takahashi T, et al. Developmental defects of lymphoid cells in Jak3 kinase-deficient mice. Immunity. 1995; 3:771-782
[18] Grossman WJ, Verbsky JW, Yang L, et al. Dysregulated myelopoiesis in mice lacking Jak3. *Blood.* 1999; 94:932-939
[19] Notarangelo LD, Candotti F. JAK3-deficient severe combined immunodeficiency. Immunol Allergy Clin N Am 20:97-111, 2000

Administration of tofacitinib to CIA mice significantly reduced the incidence and severity of arthritis symptoms (50% effective dose (ED_{50}): 16 mg/kg twice daily (bd); 29 mg/kg once daily), with JAK1/3 and JAK1/2 inhibition (ED_{50} 3 and 5 mg/kg twice a day, respectively) preferentially over JAK2 (ED_{50} >100 mg/kg twice a day). Administration of 50 mg/kg bd reduced the severity of paw inflammation by day 4, and decreased histologically assessed inflammation by day 7. Between days 1-7, this dose decreased STAT1 activation, NK cell surface, macrophage surface, and B cell surface markers, as well as major cytokines, with some of the effects starting within 4 h. Administration of a single 10 or 50 mg/kg dose demonstrated that cytokine activity was inhibited starting within 4 h, and that the activity had returned to basal levels between 12-24 h post dose.

Administration of tofacitinib to AIA rats reduced paw oedema or volume, peripheral blood neutrophil count (PBNC), and reduced plasma IL-6, IL-17 and α2-macroglobulin. Plasma concentrations of IL-6, IL-17, STAT1 responsive genes, and paw tissue concentrations of IL-6 were reduced as early as 4 h after dosing onset, and concentrations returned to basal levels by 24 h. Genes associated with NK cells were significantly decreased within day 1 of treatment. Three or four to seven days after onset of therapy, tofacitinib decreased inflammation, osteoclast-mediated bone resorption, ED-1 (CD68) and CD3+ cells in joints, gene sets corresponding to macrophage, B cells, T cells and osteoclasts, repressed elevated basal lipid levels in AIA peritoneal macrophages, attenuated the enhanced lipid loading capability in AIA macrophages, and repressed cholesterol ester percentage. Tofacitinib also increased plasma cholesterol (mostly high density lipoprotein-cholesterol, HDL-C), apolipoprotein A1 (apoA1), plasma cholesterol ester, and in vivo rate of cholesterol esterification in AIA rats, without any effect on efflux of cholesterol from tissues to the plasma compartment. However, repeat dose toxicology studies in healthy rats and cynomolgus monkeys dosed with tofacitinib showed no noteworthy effects on serum cholesterol or triglycerides.

Secondary pharmacodynamics and safety pharmacology

In secondary activity tests for 118 receptors, ion channels and enzymes, tofacitinib significantly inhibited FLT-1 kinase (vascular endothelial growth factor receptor 1 (VEGFR1); IC_{50} = 3.7 μM), MT3 (ML2; IC_{50} = 5.3 μM), Ca^{2+}/calmodulin-dependent protein kinase (CaMK2α, IC_{50} = 12 μM) and LynAKinase (IC_{50} = 2.3 μM).

After 2 days of oral treatment with 5 mg/kg bd, tofacitinib reduced the reticulocyte count of cynomolgus monkeys by 33%. When administered starting 2 days before treatment with erythropoietin (EPO) and continuing for 15 days, tofacitinib attenuated EPO-induced increases in reticulocyte counts.

Specialised safety pharmacology studies examined potential effects on the central nervous system (CNS), cardiovascular (CV), renal and gastrointestinal systems. The oral route of administration was selected for these studies since it is the intended route of clinical exposure.

Tofacitinib inhibited the human ether- à -go-go related gene (hERG) current amplitude at concentrations of ≥ 10 μM (≥ 3120 ng/mL). The IC_{50} was > 100 μM (> 31240 ng/mL). There was no significant effect of tofacitinib at in vitro concentrations of up to 10 μM on cardiac action potentials evoked in isolated dog Purkinje fibers. Overall, the in vitro studies suggest that tofacitinib has minimal potential for delaying cardiac repolarisation in clinical use.

In cardiopulmonary studies in male monkeys, male rats and female rats, tofacitinib administration caused increased heart rate (HR) at 300, 100, and ≥ 10 mg/kg, respectively (up to 142 times the unbound Cmax in humans), which was accompanied by decreased arterial pressure in male and female rats, but not in monkeys.

No electrocardiogram (ECG) changes were identified in monkeys in the safety pharmacology study, or in the 4 or 39 week toxicity studies.

Administration of ≥ 30 mg/kg tofacitinib to male rats inhibited gastric emptying and reduced intestinal motility. At a dose of 30 mg/kg, the unbound $AUC_{0\text{-}24\ h}$ in rats represented an exposure margin of about 20 relative to the human unbound $AUC_{0\text{-}24\ h}$ at a dose of 10 mg bd.

Male rats displayed anuria and an increase in potassium excretion following 100 mg/kg oral tofacitinib (103 times unbound Cmax for the 10 mg bd human dose) but not 10-30 mg/kg (Cmax relative exposure of at least 20). CNS symptoms, including mild seizures, were observed in male mice at ≥ 100 mg/kg oral (exposure ratio of ≥ 45, unbound Cmax) but not at ≤ 32 mg/kg oral.

Overall, the results demonstrated significantly higher affinity and selectivity of tofacitinib for JAK3 and JAK1 dependent signalling, with moderate functional selectivity over JAK2/TyK2 and JAK2 homodimer signalling. In humans, the observed unbound Cmax of 71 ng/mL represents a concentration of 227 nM, meaning that JAK1/3 signalling will be inhibited at therapeutic doses. Inhibition of JAK1 when dimerized with JAK2 or TyK2 will also result in inhibition of signalling by cytokines such as IFN gamma, IL-6, G-CSF, IFN alfa and IFN beta. Moreover, signalling via JAK2 dimers by growth factors such as EPO and prolactin may be expected to be inhibited at higher tofacitinib exposure levels.

Pharmacokinetics

The absorption, distribution, metabolism, and excretion of tofacitinib were evaluated mostly in rats and monkeys. Dogs were used in early nonclinical studies.

Tofacitinib had low to moderate protein binding in the plasma of all species. Given the species differences in plasma protein binding, exposure margins were calculated using unbound concentrations. Plasma protein binding was similar between mice (33%), monkeys (35%), and humans (39%), whereas protein binding in dogs was only 20%. Rat plasma protein binding varied with concentration (free fraction increased with concentration, between 6 and 31%), so a composite rat free fraction of 0.85 (15% binding) was used to calculate free fraction exposure margins. Protein binding was not determined for rabbits. Tofacitinib distributes equally between red blood cells and plasma, binding predominantly to albumin (50%) without binding to α1-acid glycoprotein.

Tofacitinib was rapidly absorbed in rats, rabbits, dogs, monkeys and humans, with peak plasma concentrations typically reached within 30 min of oral administration (slightly slower in monkeys: Tmax 1.2–1.5 h). Oral bioavailability was > 40% in laboratory animals tested (43% in rats and dogs, 48% in monkeys and 74% in humans). Plasma exposure increased with dose in all species. The plasma half-life in animals was short, ranging from 0.6 to 2.8 h compared with an elimination half-life in humans of about 3.5 h.

Distribution of radioactivity was rapid in rats that received radiolabelled (^{14}C)-tofacitinib oral, with Tmax of 0.5 to 1 h except for ocular tissue containing melanin (Tmax = 12 h). Tissue concentrations of radioactivity were equal to or higher than that in blood in most tissues at 30 min, except for the testis, adipose tissue, CNS and vitreous body (Tissue:Plasma (T:P) ratios at 30 min of 0.3, ≤ 0.2, ≤ 0.1 and 0.04, respectively). This suggested limited distribution across the blood-brain barrier. Elimination was almost complete by 24 h.

The metabolism of tofacitinib was extensive, with primary metabolic pathways involving N-demethylation, oxidation of the piperidine ring, oxidation of the pyrrolopyrimidine ring, oxidation of the piperidine ring side chain, and glucuronidation. All of these pathways operated in monkeys (most in rats), and their combined actions produced a complex array of metabolites (≥ 23 distinct in vivo metabolites identified). The unchanged drug was the

major radiolabelled compound detected in the plasma of humans (69%), monkeys and rats after oral administration of ^{14}C-labelled tofacitinib. Tofacitinib's metabolism in humans was most closely modelled by monkeys, with all human circulating metabolites also identified in monkey plasma.

In vitro experiments with recombinant human enzymes indicated that multiple cytochrome P450 (CYP) enzymes are involved in the metabolism of tofacitinib, with CYP3A4 being the isoform chiefly responsible (only a minor contribution from CYP2C19). CYP isoforms were only weakly inhibited by tofacitinib (IC_{50} > 30 μM). The potential for drug interactions with compounds metabolised by CYP isoforms is low.

Excretion of radioactivity following oral dosing with ^{14}C-tofacitinib was primarily via the urine in humans, monkeys and rabbits, and via the faeces in mice. Excretion in rats was only slightly higher in urine than in faeces. Biliary excretion of ^{14}C-tofacitinib-derived radioactivity was observed in the only species tested, monkeys.

Comparisons of the PK profiles of tofacitinib in the laboratory animal species used in the pivotal repeat dose toxicity studies (rats and monkeys) and humans indicate that sufficient similarities exist to allow them to serve as appropriate models for tofacitinib toxicity in humans. Of these, the monkey is better suited as all the circulating metabolites in humans were detected in the monkey, while metabolites M8, M11, M20, M22, M31 were not detected in rat plasma, urine or faeces.

Pharmacokinetic drug interactions

Tofacitinib is a substrate for P-glycoprotein (P-gp) but not for breast cancer resistance protein (BCRP, ABCG2) or human organic cation transporters (hOCT1, hOCT2). It is a low potency inhibitor of CYP isoforms (IC_{50} > 30 μM, 132-fold the Cmax for free tofacitinib in patients at the clinical dose), P-gp (IC_{50} = 311 μM), human organic anion-transporting polypeptide 1B1 (hOATP 1B1; IC_{50} = 55.3 μM), and human organic cation transporter in kidney (hOCT2; IC_{50} = 150 μM), but does not inhibit human uridine diphosphate glucuronosyltransferases (hUGT).

Overall, the potential for tofacitinib to experience or cause drug interactions at cellular transporters is negligible at therapeutic concentrations.

Toxicology

Acute toxicity

Tofacitinib displayed a low level of acute toxicity. No acute toxicity was observed following intravenous (IV) administration of 3 mg/kg tofacitinib to monkeys.

Repeat-dose toxicity

The comprehensive nonclinical program for tofacitinib consisted of toxicology studies (oral only) in rodents of up to 2 years in duration and nonhuman primates for up to 39 weeks duration. Pivotal nonclinical toxicology studies were conducted in rats (6 month, doses of 0, 1, 10, 100 mg/kg/day) and cynomolgus monkeys (9 months, doses of 0, 0.5, 2, 10 mg/kg/day).

The duration of the pivotal studies, the species used (rats and monkeys), group sizes and the high-dose level selected were consistent with ICH guidelines and were appropriate.

Mortality in repeat dose toxicity studies was associated with bacterial infections of the kidney, lung alveolar histiocytosis and interstitial inflammation in rats, and with lymphomas, and bacterial and viral infections in monkeys.

Relative exposure

Exposure ratios were calculated based on animal:human plasma free Cmax and free $AUC_{0\text{-}24\ h}$ values. The doses of tofacitinib used in the pivotal repeat-dose toxicity studies produced high multiples of the anticipated clinical systemic exposure (Table 1).

Table 1: Relative exposure in repeat-dose toxicity, reproductive toxicity, and carcinogenicity studies

Species Study duration	Sex	Dose mg/kg/ day	Cmax ng/mL	Free Cmax ng/mL	AUC 0-24 h ng.h/ mL	Free AUC 0-24 h ng.h/ mL	ER free Cmax	ER free AUC
Rat 6 Week	M	1	109	93	136	116	1.3	0.2
	F	1	236	201	322	274	2.8	0.4
	M+F	1	173	147	234	199	2.1	0.3
	M	10	1080	918	1850	1573	13	2.5
	F	10	2980	2533	4730	4021	36	6.5
	M+F	10	2030	1726	3290	2797	24	4.5
	M	100	8130	6911	49400	41990	97	68
	F	100	8860	7531	51200	43520	106	70
	M + F	100	7560	6426	50300	42755	91	69
Rat 6 Month	M	1	120	102	255 ($AUC_{0\text{-}8}$)	217	1.4	0.4
	F	1	382	325	710 ($AUC_{0\text{-}8}$)	604	4.6	1.0
	M+F	1	251	213	478 ($AUC_{0\text{-}8}$)	406	3.0	0.7
	M	10	1640	1394	3440	2924	20	4.7
	F	10	3040	2584	7680	6528	36	11
	M+F	10	2340	1989	5550	4718	28	7.6
	M	100	9670	8220	43200	36720	116	59
	F	100	10600	9010	68800	58480	127	94
	M+F	100	9040	7684	56000	47600	108	77

Species Study duration	Sex	Dose mg/kg/ day	Cmax ng/mL	Free Cmax ng/mL	AUC 0-24 h ng.h/ mL	Free AUC 0-24 h ng.h/ mL	ER free Cmax	ER free AUC
Rat Fertility 63 days (until GD7)	F	1	262	222.7	-	-	3.1	-
		10	3000	2550	-	-	36	-
		100	8000	6800	-	-	96	-
Rat Embryofetal Development (GD 17)	F	1	185	157	516	439	2.2	0.7
		10	2690	2287	8400	7140	32	12
		30	4900	4165	24000	20400	59	33
Rat Embryofetal Development (GD 17)	F	30	6360	5406	29400	24990	76	40
		100	9390	7982	73800	62730	112	101
		300	14400	12240	108000	91800	172	148
Rat Fertility and Development in Juvenile (Day 35 (Females) or 50 (Males))	M	1	95.3	81	148	126	1.1	0.2
	F	1	249	212	412	350	3.0	0.6
	M	10	1440	1224	2660	2261	17	3.7
	F	10	2890	2457	5620	4777	35	7.7
	M	100	7480	6358	67500	57375	90	93
	F	100	10100	8585	77200	65620	121	106
Rat 2 year Carcinogen-icity (Week 26)	M	10	1600	1360	3880	3298	19	5.3
	F	10	2840	2414	7850	6673	34	11
	M+F	10	2220	1887	5860	4981	27	8.0
	M	30	4190	3562	12600	10710	50	17
	F	30	6940	5899	30200	25670	83	41
	M+F	30	5560	4726	21400	18190	67	29
	M	75	7760	6596	44400	37740	93	61
	F	100/75*	9450	8033	68100	57885	113	94

Species Study duration	Sex	Dose mg/kg/ day	Cmax ng/mL	Free Cmax ng/mL	AUC 0-24 h ng.h/ mL	Free AUC 0-24 h ng.h/ mL	ER free Cmax	ER free AUC
Rat 3 day micronucleus test	M	250	7700	6545	47500	40375	92	65
	F	250	9850	8372.5	84600	71910	118	116
	M+F	250	8480	7208	51700	43945	102	71
Rat 7-Day Phototoxicity	M+F	10	4270	3630	8070	6860	51	11
		30	6830	5806	24900	21165	82	34
		100	12000	10200	56000	47600	144	77
Monkey 4 Week	M+F	10	194	126	2770	1801	1.8	2.9
		50	718	467	10700	6955	6.6	11
Monkey 39 Week	M+F	0.5	20	13	79	51	0.2	0.1
		2	107	70	524	341	1.0	0.6
		10	501	326	2890	1879	4.6	3.0
Monkey 39 week juvenile ($AUC_{0\text{-}12\ h}$)	M	0.5	30.3	20	28.4	18	0.28	0.03
	F	0.5	36.2	24	33.8	22	0.33	0.04
	M	2	110	72	207	135	1.0	0.2
	F	2	128	83	218	142	1.2	0.2
	M	10	427	278	1140	741	3.9	1.2
	F	10	428	278	1230	800	3.9	1.3
Mouse 6 Month Carcino-genicity	M+F	25	1640	1099	1920	1286	15	2
		75	3830	2566	7550	5059	36	8.2
		200	5480	3672	17300	11591	52	19
Rabbit Embryofetal Development (GD 19)	F	10	610	610	1470	1470	5.3	1.4
		30	2490	2490	6350	6350	21.5	6.3
		100	8220	8220	32100	32100	70.9	31.7

Species Study duration	Sex	Dose mg/kg/ day	Cmax ng/mL	Free Cmax ng/mL	AUC 0-24 h ng.h/ mL	Free AUC 0-24 h ng.h/ mL	ER free Cmax	ER free AUC
Human	-	10 mg bd	116**	71	1014**	619	-	-

ER = exposure ratio; Unbound (free) fractions: mouse 0.67, rabbit 1 (default, not determined experimentally), rat 0.85, monkey 0.65, human 0.61.* Dose was lowered from 100 to 75 mg/kg/day in Month 4 due to excessive mortality. ** Mean Cmax and $AUC_{0\text{-}24\ h}$ values were obtained from PK study PMAR-00178 for patients with RA at the maximum proposed dose of 10 mg bd. M: male; F: female; M+F: males and females; GD: gestation day.

Major toxicities

The major target organs for tofacitinib toxicity were the immune and haematopoietic organ systems. Toxicity findings included myeloid and erythroid bone marrow depletion atrophy of lymphoid organs, reductions in circulating white and red blood cells, and increased bacterial infections.

Lymphoid depletion of the spleen, thymus, bone marrow and lymph nodes was observed in rats, and lymphoid depletion of the spleen was observed in monkeys. In the pivotal rat study, histopathological changes among lymphoid tissues were seen from 10 mg/kg/day (relative exposure, 7.6), with circulating lymphocytes significantly reduced starting at this dose. A lymphoid depleting effect of tofacitinib in monkeys was apparent in the spleen in the 4 week study following treatment at 50 mg/kg/day (relative exposure, 11), a dose which caused 100% mortality in male monkeys. In a study of shorter duration (2 weeks), administration of 50 mg/kg/day to monkeys caused lymphoid depletion of the spleen, thymus, bone marrow and lymph nodes (relative exposure, 18).

In the 6 week and 6 month rat studies, a dose level of 10 mg/kg (relative exposure, ≥ 2.5) and 100 mg/kg (relative exposure, ≥ 70) produced anaemia in males and females, respectively.

In monkeys, tofacitinib caused dose-dependent decreases in red blood cell counts, starting at 0.5 mg/kg (relative exposure 0.2 and 0.3 based on Cmax in 39 week studies in adult and juvenile monkeys, respectively), and achieving statistical significance at 2 mg/kg (relative exposure 1 based on Cmax, juvenile monkey study) and 50 mg/kg (relative exposure 11 based on AUC; 4 week study). Compensatory increases in reticulocytes were observed in some of the rat and monkey studies. A direct myelotoxic effect of tofacitinib is demonstrated by findings of bone marrow lymphoid depletion in rats at ≥ 10 mg/kg/day (6-week study; relative exposure, ≥ 4.5). Bone marrow effects were not observed in monkeys up to very high doses of 50 mg/kg (relative exposure of 11 based on AUC; 4 week study).

Infections were observed in many of the animals that died during treatment. Infections were present in monkeys receiving ≥ 50 mg/kg/day for 4 weeks (11 fold the human AUC). It is expected that due to the immunosuppressive action of tofacitinib, infections may be a concern in clinical practice.

The reversibility of the tofacitinib-induced changes was investigated in a 6-week study in rats, a 4 week study in adult monkeys, and a 39 week study in juvenile monkeys. Decreased white blood cells (WBC), red blood cells (RBC), and lymphocyte counts were partially reversed in rats treated at 100 mg/kg for 6 weeks followed by a 4 week treatment-free period. Even after this period, the rats displayed small thymus and lymphoid depletion of the bone marrow.

After a treatment-free period of 26 weeks, juvenile monkeys treated with ≥ 2 mg/kg/day for 39 weeks still displayed decreased lymphocyte counts, and presented rebound increases in spleen and thymus weights in females, and of spleen in males at 2 (but not 10) mg/kg/day. Juvenile monkeys treated with 10 mg/kg/day still displayed decreases in lymphocyte subsets after the recovery period. The only persistent changes found in adult monkeys treated at 50 mg/kg/day for 4 weeks followed by a 4 week treatment-free period were increases in alanine transaminase (ALT) and aspartate transaminase (AST). These animals also showed partial recovery of RBC counts, haemoglobin, and haematocrit, and a rebound increase in lymphocytes.

Most of the effects observed in the repeat dose toxicity studies are likely to be mediated by the drug's primary pharmacological actions. Changes in bone marrow and lymphoid organ histology and haematological parameters are consistent with roles for JAK1, JAK2 and JAK3 kinases in lymphopoiesis and/or haematopoiesis.

Other toxicities

Gastric and hepatic toxicity was evident in some repeat-dose toxicity studies at high exposures. Rats receiving between 30 and 1000 mg/kg/day for 2 weeks displayed multifocal slight to moderate necrosis of the stomach, correlated with gastric enlargement (at > 50 fold the AUC in humans). Stomach distension was observed in rats receiving a single dose of 1000 mg/kg (these animals died and displayed necrosis of centrilobular hepatocytes and individual hepatocytes). Monkeys receiving 200 mg/kg/day for 2 weeks displayed gastric and intestinal dilatation, as well as red foci in the stomach (at 77 fold the AUC in humans). Events of gastrointestinal perforation have been reported in clinical trials of tofacitinib in RA, although the role of JAK inhibition in these events is unknown. The proposed PI notes that tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation.

Changes in the liver of the rats were observed after administration of ≥ 100 mg/kg/day (≥ 77 fold the AUC in humans) for between 2 weeks and 6 months. Changes comprised increased liver weights (decreased liver weights in females), hepatocellular and centrilobular hypertrophy. These changes are typical rodent adaptive responses to high oral doses of CYP-metabolised drugs and are not considered clinically relevant at such high exposure margins.

Genotoxicity

Tofacitinib displayed no mutagenic effects in the bacterial reverse mutation test, or forward mutation test in Chinese hamster ovary (CHO) cells. While a clastogenic effect of tofacitinib was seen in the human lymphocyte assay in vitro (with metabolic activation only at cytotoxic concentrations > 20000 fold the maximum anticipated human unbound Cmax), tofacitinib was negative in the same study without metabolic activation (cytotoxic concentrations equivalent to 17000 fold the unbound human Cmax). Furthermore, no clastogenicity was observed in vivo in the rat micronucleus test following treatment with tofacitinib at ≤ 250 mg/kg/day orally for 3 days. No mortality or clinical signs were observed in this study but toxicokinetic analysis showed that the relative exposure achieved (based on AUC) was more than 65 times that anticipated clinically at 10 mg tofacitinib bd.

The weight of evidence suggests that tofacitinib is not genotoxic.

Carcinogenicity

The carcinogenic potential of tofacitinib by the oral route was investigated in a traditional 2 year rat study and was supplemented by a 6 month study in transgenic rasH2 mice.

No treatment-related increases in tumour incidence were detected in rasH2 mice up to the high dose level of 200 mg/kg/day tofacitinib. This dose caused only limited mortality and corresponded to a relative exposure margin of 19 (based on AUC).

Group sizes and dose levels in the 2 year rat study were appropriate. Treatment-related neoplastic findings in males included benign angiomas and benign Leydig cell tumors (benign interstitial cell tumours of the testes). Females treated with tofacitinib displayed malignant hibernomas and benign thymomas.

The biological significance and the risk to humans of the increased incidence of benign angioma in male rats receiving 10 mg/kg/day (5.3 times the expected exposure in humans, based on AUC) is considered low, as these tumours showed no dose dependency and were only observed in one gender and one rodent species.

The increase in Leydig cell tumours at high relative systemic exposure margins (17 fold) in the rat study was attributed to inhibition of prolactin signalling via the JAK2/STAT5 pathway within Leydig cells which causes a decrease in Leydig cell luteinizing hormone (LH) receptor number and thus a decrease in testosterone production with a concomitant increase in circulating LH to maintain testosterone levels. This effect has also been seen with other drugs (such as dopamine agonists) affecting prolactin in rats and has been shown to be rodent-specific and therefore not relevant to humans.

Hibernoma (malignancy of brown adipose tissue) incidence was increased at ≥ 30 mg/kg/day in female rats. Hibernoma incidence was not increased at 10 mg/kg/day in females (exposure margin 11; AUC) or at 75 mg/kg/day in males (exposure margin 61; AUC). A 2 week study in female rats confirmed that tofacitinib has a proliferative effect on normal brown adipose tissue at the same doses associated with increased hibernoma incidence in the 2 year study. Mechanistic studies suggested that inhibition of JAK/STAT signalling and/or increased sympathetic stimulation may have contributed to the development of hibernoma in rats. Given that hibernoma incidence was increased only at high exposure margins in one rodent species and one sex suggest that tofacitinib does pose a significant human risk for hibernoma at clinical exposures. Hibernoma in humans is a rare, benign tumour that does not recur with complete excision (Furlong et al., 2001[20]).

A significant increase in the incidence of benign thymoma was observed in female rats receiving the highest dose of 100 (reduced to 75) mg/kg/day (exposure margin 94; AUC). Thymomas are rare in rodents and humans, and although the mechanism of their development is unknown, the very high exposure suggests that these tumours are not of clinical concern.

Lymphomas were observed in 3 of 8 adult monkeys and 0 of 14 juvenile monkeys dosed with tofacitinib at 10 mg/kg/day (3 times the expected exposure in humans, based on AUC).

Treatment related lymphomas were observed in 3 of 8 high dose (10 mg/kg/day) adult animals in the 39 week monkey study (3 times the expected exposure in humans, based on AUC). Two of these cases were confirmed lymphocryptovirus (LCV)-related B cell lymphomas, while the remaining one was confirmed to be a T cell lymphoma. In a renal allograft study, 1 of 8 animals receiving tofacitinib and mycophenolate mofetil had a single enlarged mesenteric lymph node with a macroscopic (no histopathological evaluation) diagnosis of lymphoma (Borie et al., 2005[21]). No lymphomas were observed in the tofacitinib 39 week juvenile monkey study at the same doses as in adult monkeys. The LCV associated lymphomas observed in the 39 week monkey study were considered secondary

[20] Furlong MA, Fanburg-Smith JC, Miettinen M. The morphologic spectrum of hibernoma: a clinicopathologic study of 170 cases. Am J Surg Pathol 2001; 26(6):809-14
[21] Borie D, Larson M, Flores M, et al. Combined use of the JAK3 inhibitor tofacitinib with mycophenolate mofetil to prevent kidney allograft rejection in non-human primates. Transplantation. 2005; 80(12): 1756-64

to immunosuppression. The PI document warns about the possibility of patients developing lymphomas. Follicular lymphocyte hyperplasia was observed at all dose levels in the 39 week adult monkey study. Based on the morphology, which resembled normal reactive follicular lymphoid hyperplasia, and the lack of staining for LCV, this lymphocyte hyperplasia is not considered a precursor of lymphomas.

Reproductive toxicity

Reproductive and developmental effects were assessed in fertility, peri/post natal development, and embryofetal developmental studies in rats as well as an embryofetal developmental study in rabbits. Tofacitinib was shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility, parturition, and peri/postnatal development.

In rats, tofacitinib had no effects on male fertility, sperm motility, or sperm concentration at doses up to 100 mg/kg/day (no observed adverse effect level (NOAEL), exposure margin 93; AUC). However, tofacitinib had significant effects on the female fertility of rats (decreases in pregnancy rate, corpora lutea, implantation sites, viable fetuses; increases in early resorptions) at ≥ 10 mg/kg/day (exposure margin ≥ 36; Cmax), with a NOAEL for female fertility of 1 mg/kg/day (exposure margin 3; Cmax).

In an embryofetal development study in rats given 30, 100, or 300 mg/kg/day, maternotoxicity was evident at doses ≥ 100 mg/kg/day with increases in postimplantation loss (early and late resorptions leading to a reduction in viable fetuses) and decreased uterine weight. Multiple fetal visceral and skeletal malformations were observed at 100 mg/kg/day (exposure margin ≥ 100; AUC). The NOAEL for maternal and developmental toxicity of 30 mg/kg/day corresponds to an exposure margin of 40 (based on AUC).

In an embryofetal development study in rabbits, maternal toxicity was not observed at concentrations of up to 100 mg/kg/day (exposure margin 32; AUC). Fetal developmental effects consisting of multiple visceral and skeletal malformations were observed at ≥ 10 mg/kg/day (exposure margin ≥ 1.4; AUC).

A perinatal/postnatal rat study demonstrated no effect of tofacitinib on sexual maturation or the ability of the offspring (F1 generation) rats to learn, mate, and produce viable F2 generation fetuses at 10 mg/kg/day (exposure margin 4.5; AUC). At 50 mg/kg/day (exposure margin 23 based on body surface area), the number of delivered pups and liveborn pups were reduced. Reductions in live litter size, pup body weights and postnatal survival (all pups died between days 1 and 4 postpartum in litters delivered from 14/21 dams, and 16 dams were euthanised because of no surviving pups) were observed.

Tofacitinib was secreted in the milk of lactating rats.

No data regarding placental transfer were submitted. This is acceptable as the conduct of rat and rabbit placental transfer studies would not change or clarify the current embryofetal development risk assessment given that teratogenicity has been clearly observed in rats and rabbits.

Pregnancy classification

For the use of tofacitinib in pregnancy the sponsor has proposed Pregnancy Category B3, which is defined as *drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals using drugs in this Category have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans*.

The Australian Pregnancy Category for tofacitinib should be changed to Category D, as the nonclinical data (particularly the low relative exposure margin to the embryofetal development NOAEL in the rabbit study) are more consistent with the Category D: *Drugs which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.*

It is also noted that Pregnancy Categories C[22] and D have been used for other "-inib" drugs such as the tyrosine kinase inhibitors.

Haemolysis

No haemolysis or precipitation was observed following incubation of tofacitinib with heparinised human whole blood (at concentrations up to 0.5 mg/mL) or plasma (≤ 0.5 mg/mL), for 30 minutes.

Local tolerance (eyes and skin)

Tofacitinib was found not to be a contact sensitiser in mice. Tofacitinib did not induce significant or irreversible damage to the eye in rabbits and monkeys, and was not an irritant to the skin in rabbits and minipigs. It is not expected that local tolerance of tofacitinib will be a concern for patients.

Phototoxicity

Tofacitinib displayed negative phototoxicity in vitro in the 3T3 Neutral Red uptake assay. No ocular or cutaneous changes were identified in the in vivo phototoxicity study in pigmented rats, or any of the repeat-dose toxicity studies.

Impurities

The proposed specifications for impurities in the drug substance which were above the ICH qualification thresholds have been adequately qualified.

Paediatric use

Tofacitinib is not proposed for paediatric use. Studies in juvenile rats and monkeys were submitted and did not indicate adverse effects on developing tissues.

Nonclinical summary and conclusions

- An extensive and appropriate dossier of nonclinical studies was submitted according to the relevant ICH guidelines, with pivotal studies performed under GLP, and non-GLP studies were adequately documented.
- Tofacitinib is a potent inhibitor of the JAK family, with a high degree of selectivity over other kinases, and moderate functional selectivity for inhibition of JAK1 and JAK3 over JAK2. Efficacy in animal models of arthritis is attributed to inhibition of JAK1/3 and to a lesser extent JAK1/2, which interrupts the intracellular signalling of several cytokines that modulate multiple aspects of the immune response. JAK1/3 signalling will be inhibited at therapeutic doses.

[22] Definition of Category C for use drugs in pregnancy: *Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details*.

- Tofacitinib when given orally displayed efficacy in vivo, in both the mouse CIA model and the rat AIA model, with a reduction in both the incidence and severity of arthritis symptoms and inflammatory markers. Pharmacokinetic/pharmacodynamic (PK/PD) modelling of the CIA study suggested that efficacy is primarily derived from JAK1/3 inhibition and not JAK2 inhibition.
- In secondary PD studies in cynomolgus monkeys tofacitinib reduced reticulocyte counts and attenuated EPO-induced increases in reticulocyte counts, suggesting possible inhibition of JAK2 effects on EPO signalling at relative exposure levels only a few fold above those anticipated clinically. Safety pharmacology studies did not reveal any particular concern for adverse effects of tofacitinib on CV (including potential for delayed repolarisation), CNS, renal or gastrointestinal systems at therapeutic doses.
- Tofacitinib was rapidly absorbed in rats, rabbits, dogs, monkeys and humans, with peak plasma concentrations typically reached within 30 min of oral administration (slightly slower in monkeys: 1.2–1.5 h). Oral bioavailability was > 40% in laboratory animals tested, and 74% in humans. Plasma exposure increased with dose in all species. The plasma half-life was short, ranging from 0.6 to 2.8 h.
- Tofacitinib displayed rapid tissue distribution following oral administration but transfer across the blood-brain barrier was limited. Elimination was almost complete by 24 h. Plasma protein binding was similar in mice (33%), monkeys (35%) and humans (39%), lower in dogs (20%), and varied with concentration in rats such that a composite free fraction of 0.85 (15% binding) was used to calculate unbound exposure margins. Tofacitinib binds predominantly to albumin and does not appear to bind to α1-acid glycoprotein, and distributes equally between red blood cells and plasma.
- The metabolism of tofacitinib was extensive, with primary metabolic pathways involving N-demethylation, oxidation of the piperidine ring, oxidation of the pyrrolopyrimidine ring, oxidation of the piperidine ring side chain, and glucuronidation. All of these pathways operated in monkeys (most operate in rats), and their combined actions produced a complex array of metabolites (≥ 23 distinct in vivo metabolites identified). The unchanged drug was the major radiolabelled compound detected in the plasma of humans (69%), monkeys and rats after oral administration of ^{14}C-labelled tofacitinib. Tofacitinib's metabolism in humans was most closely modelled by monkeys, with all human circulating metabolites also identified in monkey plasma. Excretion following oral dosing was primarily via the urine in humans, monkeys and rabbits, via the faeces in mice, and mixed in rats.
- Multiple CYPs are involved in the metabolism of tofacitinib, with CYP3A4 being the isoform chiefly responsible (and only a minor contribution from CYP2C19). Tofacitinib is a substrate and a weak inhibitor of P-gp, but is not a substrate for the breast cancer resistance protein (BCRP, ABCG2), or the uptake transporters hOCT1 or hOCT2. Tofacitinib did not inhibit human OATP1B3 or UGTs, and only weakly inhibited hOATP1B1 and human organic cation transporter (hOCT2) in vitro. Significant drug interactions are unlikely at therapeutic plasma concentrations.
- Tofacitinib displayed a low level of toxicity in acute studies. No acute toxicity was observed following IV administration of 3 mg/kg in monkeys.
- Pivotal repeat dose toxicity studies included a 6 month study in rats and a 9 month study in adult monkeys. The high-dose level in the pivotal monkey study (10 mg/kg/day; exposure margin 3.0; unbound AUC) produced excessive mortality while the high dose in the rat study did not produce excessive mortality or suppress body weight gain at high exposure margins (> 70 times; unbound AUC).
- Major toxic effects were evident in the spleen, thymus and lymph nodes (lymphoid depletion), and bone marrow (lymphoid depletion, hypocellularity and associated

anaemia). Effects in a number of other organs, including the liver and gastrointestinal tract, were also observed. Most of the changes seen in tofacitinib-treated animals are recognised to be consistent with the drug's primary pharmacological actions, inhibition of JAK1/3 or JAK2. Toxic effects were partially reversible upon treatment withdrawal.

- Other nonclinical studies revealed the presence of bacterial and viral infections, as well as the development of lymphomas likely due to the immunosuppressive effects of tofacitinib. Immunosuppression and the development of lymphomas are recognised risks for tofacitinib and are described in the PI. Studies in juvenile rats and monkeys were submitted and did not indicate adverse effects on developing tissues.
- The potential genotoxicity of tofacitinib was examined in an adequate battery of tests. Tofacitinib was not mutagenic in vitro in the bacterial reverse mutation assay, the forward mutation test in mammalian cells, or the unscheduled DNA synthesis test. It displayed clastogenicity in the in vitro mammalian chromosomal aberration assay in the presence of metabolic activation, but no clastogenic effect was observed in the in vivo chromosomal aberration assay conducted in rats. The weight of evidence suggests that tofacitinib is not genotoxic.
- Carcinogenicity was assessed in a 6 month rasH2 transgenic mouse study and a conventional 2 year rat study. No treatment-related neoplasia was observed in rasH2 transgenic mice. Neoplastic findings in the rat study included benign angiomas and benign Leydig cell tumors in males; malignant hibernomas and benign thymomas in females. All of these treatment related tumours were considered to be of little or no relevance to humans based on mechanistic and/or exposure margin grounds.
- Reproductive and developmental effects were assessed in fertility, peri/post natal development, and embryofetal developmental studies in rats as well as an embryofetal developmental study in rabbits. No effects on male fertility, sperm motility, or sperm concentration were seen in rats at doses up to 100 mg/kg/day (exposure margin 93; unbound AUC). Tofacitinib was teratogenic in rats and rabbits, and had effects in rats on female fertility, parturition and peri/postnatal development. Observations of embryofetal lethality and teratogenicity justify the drug's placement in Pregnancy Category D. Placental transfer was not investigated but may be inferred from the observed teratogenicity. Tofacitinib was shown to be excreted in milk.
- Tofacitinib did not cause haemolysis, contact sensitisation, or irritation (including phototoxicity) to the eye and skin.

Conclusions and recommendation

- Antirheumatic effects of tofacitinib were demonstrated in the mouse CIA model and the rat AIA model. While the efficacy of tofacitinib is likely to be mediated by JAK1/3 inhibition, secondary pharmacology studies suggested a limited specificity relative to JAK2 inhibition.
- The main targets of tofacitinib's toxicity were the lymphopoietic and haematopoietic systems. The observed effects were consistent with the drug's primary pharmacological actions either via inhibition of JAK1/3 (decreases in total lymphocytes, T cells and NK cells) or inhibition of JAK2 (decreases in RBC parameters and platelets).
- The development of bacterial and viral infections, as well as the development of lymphomas, were considered secondary to immunosuppression and are acknowledged potential risks of tofacitinib treatment in patients.

- Tofacitinib was shown to be teratogenic in rats and rabbits. Observations of embryofetal lethality and teratogenicity justify the drug's placement in Pregnancy Category D.
- The weight of evidence suggests that tofacitinib is not genotoxic and does not pose a direct carcinogenicity concern.
- Overall, the nonclinical data support the chronic use of tofacitinib monotherapy for the treatment of RA. In the absence of nonclinical data to support the combination use with MTX or other nonbiologic DMARDS, the risk-benefit assessment of combination use will have to be made from the clinical data.

Revisions were recommended to nonclinical statements in the draft PI; details of these are beyond the scope of the AusPAR.

IV. Clinical findings first and second rounds

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2 (Round 1 and 2 CER).

Introduction

This submission proposed to register tofacitinib citrate 5 mg and 10 mg[23] tablets. The proposed indication is:

> *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. Xeljanz can be used alone or in combination with DMARDS, including methotrexate.*

Clinical rationale

The sponsor has developed tofacitinib as an immune modulatory agent for the treatment of RA. Rheumatoid arthritis is a debilitating condition that has high morbidity and increases mortality in comparison with the healthy population. There is currently no cure for RA and treatments are aimed at decreasing symptoms, improving physical wellbeing and preventing disease progression. There are currently three main classes of agents for treating RA: NSAIDs, corticosteroids, and DMARDs. All of these drugs have significant adverse effects and incomplete efficacy. Hence, there is considerable scope for improving the treatment of RA.

Guidance

The sponsor consulted with the TGA prior to submission.

Contents of the clinical dossier

The clinical dossier represents a complete clinical development program. The submission contained the following clinical information:

- 23 clinical pharmacology studies, including 20 that provided PK data and three additional studies that provided PD data.
- Two population PK analyses.

[23] The proposal to register the 10 mg tablets was withdrawn by the sponsor after the Third Round clinical evaluation

- Five pivotal efficacy/safety studies.
- Five dose-finding studies.
- Two long term follow-on studies.
- An Integrated Summary of Efficacy, an Integrated Summary of Safety, and ten analyses of combined data.
- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The studies presented in the submission are stated to have been conducted according to good clinical practice (GCP) principles. The study reports are consistent with adherence to GCP.

Pharmacokinetics

Studies providing PK data

Table 2 shows the studies relating to each PK topic.

Table 2: Submitted PK studies.

PK topic	Subtopic	Study ID
PK in healthy adults	Effect of food on the bioavailability of tofacitinib	Study A3921005
	Effect of food on the bioavailability of tofacitinib	Study A3921076
	†Absolute bioequivalence of single doses of tofacitinib formulations intended for marketing and those used in the studies	Study A3921075
	Single dose PK of tofacitinib	Study A3921077
	Single dose PK of tofacitinib	Study A3921002
	Single dose PK of tofacitinib	Study A3921010
	Multi-dose PK of tofacitinib	Study A3921036
	Multi-dose PK of tofacitinib	Study A3921065

PK topic	Subtopic	Study ID
PK in special populations	PK in Subjects with psoriasis, Multi-dose §PK in Subjects with Rheumatoid arthritis	Study A3921003
		Study A3921013
	PK in Subjects with Renal impairment	Study A3921004
	PK in Subjects with Renal impairment	Study A3921006
	PK in Subjects with Hepatic impairment	StudyA3921015
PK interactions	Effect of Fluconazole on tofacitinib	Study A3921014
	Effect of Tacrolimus, cyclosporine on tofacitinib	Study A3921020
	Effect of Ketoconazole on tofacitinib	Study A3921054
	Effect of Rifampicin on tofacitinib	Study A3921056
	Effect of tofacitinib on Midazolam	Study A3921059
	Effect of tofacitinib on Ethinyloestradiol/ levonorgestril	Study A3921071
	Effect of tofacitinib on Metformin	Study A3921143
Population PK analyses	§PK in the Target population	Study PMAR-00178
	PK in Healthy volunteers	Study PMAR-00210

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

Summary of PK study findings

- Food increased the total exposure to tofacitinib by 15% in Study A3921005 and by 6% in Study A3921076 but slowed oral absorption and decreased Cmax by around 30% in both studies.
- The formulations used in development and those intended for marketing were demonstrated to be bioequivalent in Study A3921075.
- The absolute bioavailability of tofacitinib was 74%, and following intravenous dosing, the geometric mean (coefficient of variation (CV%)) for clearance was 412.3 (19%) mL/min, volume of distribution at steady state (Vss) was 87.08 (16%) L, and t½ was 3.523 h (9%) (Study A3921077). Following oral administration, the PK parameters for tofacitinib were dose proportional in the range 3 mg to 100 mg (Study A3921002).
- Approximately 30% of a tofacitinib dose was excreted unchanged in the urine. The remaining elimination was as urinary metabolites (50% of dose) and faecal parent drug and metabolites (14%) (Study A3921010). Mean urinary clearance of unchanged drug was approximately 150 mL/min and was not affected by dose or race (Study A3921036). With multiple dosing the geometric mean (coefficient of variation (CV%))

accumulation ratio was 1.15 (10%) (Study A3921036) and in a Han Chinese population it was 1.036 (10%) (Study A3921065).

- In subjects with medically stable psoriasis, there appeared to be some accumulation with multiple dosing with the mean accumulation ratios ranging from 0.974 to 1.62. AUC and Cmax were mostly dose proportional. The mean unbound renal clearances of tofacitinib were slightly greater than the glomerular filtration rate (GFR) indicating some active renal secretion of tofacitinib. The mean percent of administered dose excreted unchanged in the urine ranged from 18.3% to 27.2%.
- In subjects with RA there was no apparent change in the PK parameters of tofacitinib in combination with MTX (Study A3921013). However, there was a 10% decrease in MTX AUC_{24} h and 13% decrease in Cmax in combination with tofacitinib. This is unlikely to be clinically significant.
- In mild renal impairment $AUC_{0-\infty}$ was increased by 37% but Cmax was not significantly increased (Study A3921006). In moderate renal impairment $AUC_{0-\infty}$ was increased by 43% but Cmax was not significantly increased. In severe renal impairment $AUC_{0-\infty}$ was increased by 123% and Cmax was increased by 18%. Clearance of tofacitinib was impaired in subjects with end stage renal disease, but tofacitinib was found to be dialysable (Study A3921004). The fraction unbound was 0.4.
- There was no clinically significant difference in $AUC_{0-\infty}$ or Cmax between normal subjects and those with mild hepatic impairment (Study A3921015). However, there was a 65% increase in $AUC_{0-\infty}$ and a 49% increase in Cmax in subjects with moderate hepatic impairment.
- In healthy subjects AUC increased in the fed state and Cmax decreased (Study PMAR-00210). AUC and Cmax were higher in females and with Asian race. Cmax increased with lower weight. However, age did not have a significant effect on the PK parameters. However, there may be some correlation between these covariates that may have been eliminated if a stepwise approach had been used in the model building.
- In subjects with RA, apparent clearance (CL/F) increased with increasing creatinine clearance (Study PMAR-00178). Age, weight, gender and race did not have significant effects on CL/F.
- The following drug interactions were investigated:
  - In combination with fluconazole, tofacitinib $AUC0_{-\infty}$ increased by 79% and Cmax by 27% (Study A3921014). Plasma t½ increased from 2.97 h to 4.00 h. CL/F decreased from 31.7 L/h to 17.2 L/h. The proportion of the dose recovered unchanged in urine increased from 26.0% to 30.9%, but renal clearance decreased from 7.57 L/h to 5.24 L/h (Study A3921014). These data indicate that fluconazole exhibited clinically significant inhibition of both metabolic clearance and renal clearance (possibly by inhibiting the active transport of tofacitinib).
  - Concomitant tacrolimus increased the $AUC_{0-\infty}$ by 21% and decreased Cmax by 9% (Study A3921020).
  - Concomitant cyclosporine increased $AUC_{0-\infty}$ by 73% and decreased Cmax by 17% (Study A3921020).
  - Ketoconazole increased $AUC_{0-\infty}$ by 103% and increased Cmax by 16% (Study A3921054).
  - Rifampicin decreased $AUC_{0-\infty}$ by 84% and Cmax by 74% (Study A3921056).
  - Tofacitinib did not exhibit a clinically significant effect on the PK of midazolam (Study A3921059).

- There was no clinically significant effect of tofacitinib on the $AUC_{0-\infty}$ of either ethinyloestradiol or levonorgestril, but the Cmax of ethinyloestradiol was decreased by 10% and the Cmax of levonorgestril was increased by 12% (Study A3921071)
- There was no clinically significant effect of tofacitinib on the PK of metformin (Study A3921143)

Evaluator's overall conclusions on PKs

The PKs of tofacitinib have been satisfactorily described in the development program except for the following unresolved issues:

- There were few elderly subjects in the PK analyses. Hence clearance in subjects in the older age groups has not been satisfactorily examined.
- Inhibition of glucuronidation has been reported with imatinib, another tyrosine kinase inhibitor, sufficient to lead to potentially serious interactions with drugs such as paracetamol. As yet it is not known whether this could be a class interaction. Hence, effects upon glucuronidation should be examined.
- The mechanism for active renal secretion of tofacitinib has not been determined. Hence there are potential interactions that have not been excluded.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 3 shows the studies relating to each PD topic. None of the PD studies had deficiencies that excluded their results from consideration.

Table 3: Submitted pharmacodynamics studies.

PD Topic	Subtopic*	Study ID
Primary Pharmacology	Effect of tofacitinib on interleukin expression	Study A3921002
	Effect of tofacitinib on haemopoietic cells	Study A3921003
Secondary Pharmacology	Effect of tofacitinib on QTc (thorough QT study)	Study A3921028
	Effect of tofacitinib on renal function	Study A3921033
	Effect of tofacitinib on plasma lipids	Study A3921036
	Effect of tofacitinib on plasma lipids	Study A3921109

* Indicates the primary aim of the study.

Evaluator's conclusions on PDs

- The PD data demonstrated effects on lymphocyte subsets but it is not clear how these changes relate to effect. There were decreases in neutrophil, reticulocyte and platelet counts of between 30% and 40% at tofacitinib doses of 30 mg bd and 50 mg bd.
- Tofacitinib does not have significant QTc prolongation effects.
- Tofacitinib 15 mg bd for two weeks did not alter renal function in healthy volunteers.
- In the Phase I studies there did not appear to be significant changes in plasma lipids but these studies were of short duration (up to 2 weeks). However, in longer duration studies there were significant elevations in HDL, low density lipoproteins (LDL) and total cholesterol. In combination with tofacitinib atorvastatin reduced total cholesterol, LDL and triglycerides, decreased in the ratio of LDL to HDL, and maintained increases in HDL and HDL particle size.

Dosage selection for the pivotal studies

The following studies were submitted:

- Study A3921019 was a Phase IIa, randomised, double blind, placebo controlled, parallel group study in subjects with RA to compare the efficacy of three dose levels of oral tofacitinib monotherapy. The study was conducted as a proof of concept and dose finding study. Subjects received tofacitinib 5, 15 or 30 mg bd, or placebo bd.
- Study A3921025 was a Phase IIb, randomised, double blind, placebo controlled, parallel group dose-finding study of tofacitinib as add-on therapy to MTX in subjects with active RA. Subjects received tofacitinib 1, 3, 5, 10 or 15 mg bd; tofacitinib 20 mg once daily; or placebo bd.
- Study A3921035 was a Phase IIb, randomised, double blind, placebo controlled, active comparator (adalimumab), parallel group study to characterise the dose-response of tofacitinib over the range of 1 to 15 mg bd compared with adalimumab or placebo in subjects with RA.
- Study A3921039 was a Phase II, multi-center, randomised, placebo controlled, parallel group, double blind study to evaluate the dose response of tofacitinib in the range 1 to 10 mg in Japanese subjects with RA.
- Study A3921040 was a Phase II, multi-center, randomised, double blind, placebo controlled, parallel group dose finding study of tofacitinib 1-15 mg bd monotherapy compared with placebo bd in Japanese subjects with RA.

In addition, a number of studies were performed using the Phase II data to make predictions pertinent to the Phase III study program.

Evaluator's conclusions on the dose finding studies

The sponsor evaluated the dose response relationships for tofacitinib satisfactorily prior to dose selection for the Phase III studies.

In monotherapy the dose range 5 mg to 30 mg bd was investigated in Study A3921019 and efficacy appeared to peak at the 15 mg dose. For American College of Rheumatology 20% improvement in disease activity criteria (ACR20) the response rate at Week 6 was 81.16% in the 15 mg group. In Study A3921035, that studied the dose range 1 mg to 15 mg bd, ACR20 response at Week 12 peaked in the 10 mg group at 75.41%, with a slight increase to 75.44% in the 15 mg group. In Study A3921040, in Japanese subjects, the dose range 1 mg to 15 mg bd was evaluated in monotherapy and for the primary efficacy outcome

measure, ACR20, efficacy was greatest with the 15 mg dose level at 90.74%. However, for ACR70, ACR90, painful joint count, Patient's and Physician's Global Assessments, DAS-4(ESR) and FACIT score the greatest effects were at the 10 mg dose level.

In combination with MTX, the dose range 1 mg to 15 mg bd was studied in Study A3921025 and the peak response for ACR20 was 58% at the 10 mg dose level at Week 12. In Study A3921039, tofacitinib in the dose range 1 mg to 10 mg bd was evaluated in Japanese subjects and for ACR20 all active treatment groups were superior to placebo but peak effect was at the 5 mg dose level.

In addition, the sponsor performed a number of combined studies using Phase I and Phase II data to predict the dose response relationships for efficacy and for adverse effects. These studies also supported the choice of the 5 mg and 10 mg bd regimens for adopting into the Phase III trials.

Efficacy

Studies providing efficacy data

Pivotal efficacy studies in combination with MTX

- Study A3921032 was a multicentre, Phase III, randomised, 6 month, double blind, 3 month, placebo controlled, parallel-group efficacy and safety study of tofacitinib as add-on therapy to MTX in subjects with RA. Inclusion criteria included "at least one approved TNF-inhibiting biologic agent administered in accordance with its labelling recommendations was inadequately effective and/or not tolerated" (see AusPAR Attachment 2 for full inclusion criteria).
- Subjects received 5 mg tofacitinib bd; 10 mg tofacitinib bd; placebo, switched to 5 mg tofacitinib bd after 3 months; or placebo, switched to 10 mg tofacitinib bd after 3 months.

  The primary efficacy outcome measures were: ACR20 at Month 3; HAQ-DI at Month 3; and proportion of subjects with DAS28-4(ESR) < 2.6 at Month 3.
- Study A3921044 was a multicentre, Phase III, randomised, 2 year, double blind, placebo controlled, parallel group study of tofacitinib as add-on therapy to MTX in subjects with RA. The results from the first year were presented in the report as an interim analysis. The study treatments were: 5 mg tofacitinib bd; 10 mg tofacitinib bd; placebo/5 mg tofacitinib bd; or placebo/10 mg tofacitinib bd. Data for up to 12 months were provided. Subjects received 3 to 6 months of placebo and were then reallocated if there was not at least a 20% improvement in both the tender/painful and swollen joint counts as reported in the study database.

  There were four primary efficacy endpoints: ACR20 at Month 6; structure preservation as measured by the modified total Sharp score (mTSS) change from baseline at Month 6; physical function as measured by the HAQ-DI change from baseline at Month 3; and incidence of DAS28-4(ESR) < 2.6 at Month 6.
- Study A3921064 was a multicentre, Phase III, randomised, 1 year, double blind, placebo controlled, parallel group study to compare tofacitinib or adalimumab with placebo in the treatment of RA in subjects on a stable dose of MTX. The study treatments were: 5 mg tofacitinib, orally bd; 10 mg tofacitinib, orally bd; placebo/5 mg tofacitinib, orally bd; placebo/10 mg tofacitinib, orally bd; or adalimumab 40 mg by subcutaneous (SC) injection every 2 weeks.

  The primary efficacy outcome measures were: ACR20 at Month 6; HAQ-DI at Month 3; and proportion of subjects with DAS28-4(ESR) < 2.6 at Month 6

Pivotal studies as monotherapy

- Study A3921045 was a multicentre, Phase III, randomised, 6 month, double blind, placebo controlled, parallel group trial of tofacitinib as monotherapy in subjects with RA and an inadequate response to a DMARD. Study treatments were: 5 mg tofacitinib bd; 10 mg tofacitinib bd; placebo for 3 months then 5 mg tofacitinib bd; or placebo for 3 months then 10 mg tofacitinib bd.

  The study outcome measures were the same as for Study A3921032.

Pivotal studies as concurrent treatment with DMARDS

Study A3921046 was a multicentre, Phase III, randomised, 1 year, double blind, placebo controlled, parallel group study of two dose levels of tofacitinib in subjects with RA and concurrent treatment with DMARDs. The subject must have remained on at least one background traditional DMARD (tDMARD) and be dosed in accordance with the local regulatory label and willing to remain on that tDMARD throughout the course of the study. The study treatments were: 5 mg tofacitinib bd; 10 mg tofacitinib bd; placebo/5 mg tofacitinib bd; or placebo/10 mg tofacitinib bd. Study duration was for 12 months (3 to 6 months of placebo with reallocation). The study outcome measures were the same as for Study A3921032 except that the primary efficacy outcomes were measured at Month 6 (HAQ-DI primary endpoint was assessed at Month 3).

Other efficacy studies

Long term follow-on study

- A3921024/A3921041 were long term tolerability, safety and efficacy studies conducted in subjects who had completed Studies A3921019, A3921025, A3921032, A3921035, A3921044, A3921045, A3921046, A3921064, A3921069, A3921073, A3921109, A3921039, and A3921040. The efficacy outcome measures were ACR20, ACR50, ACR70, HAQ-DI score and DAS28-4(ESR). A total of 3227 subjects were included: 1321 treated with tofacitinib 5 mg bd and 1906 treated with 10 mg bd. Of these, 2019 were also on background DMARDs and 1208 were on tofacitinib monotherapy. There were 2680 (83.1%) females, 546 (16.9%) males and the age range was 18 to 86 years.

Evaluator's conclusions on efficacy

Efficacy for both dose levels (5 mg bd and 10 mg bd) was demonstrated in combination with MTX.

For ACR20:

- In Study A3921032, ACR20 was achieved by significantly more subjects in the active treatment groups: 41.67% subjects in the 5 mg group ($p = 0.0024$), 48.12% in the 10 mg ($p < 0.0001$) and 24.43% in the placebo group.
- In Study A3921044, for ACR response at Month 6, there were 51.46% responders in the 5 mg group, 61.81% in the 10 mg and 25.32% in the placebo group ($p < 0.0001$).
- In Study A3921064, for ACR20 response at Month 6, there were 51.53% responders in the 5 mg group ($p < 0.0001$ compared to placebo), 52.55% in the 10 mg ($p < 0.0001$ compared to placebo), 47.24% in the adalimumab ($p = 0.0007$ compared to placebo), and 28.30% in the placebo group.

For mTSS:

- In Study A3921044, for mTSS the change (progression) from baseline to Month 6 was significantly less in the 10 mg group than placebo: least squares (LS) mean change

0.06 compared with 0.47 (p = 0.0376); but there was no significant difference for the 5 mg dose: LS mean, 0.12.

For HAQ-DI:

- In Study A3921032, HAQ-DI decreased from baseline to a greater extent in the active treatment groups: -0.43 in the 5 mg group (p < 0.0001), -0.46 in the 10 mg (p < 0.0001) and -0.18 in the placebo group.
- In Study A3921044, for HAQ-DI the change (improvement) from baseline was greater in the tofacitinib groups: LS mean change -0.40 for 5 mg, -0.54 for 10 mg and -0.15 for placebo (p < 0.0001)[24].
- In Study A3921064, for HAQ-DI the change (improvement) from baseline was greater in the tofacitinib and adalimumab groups compared to placebo: LS mean change -0.55 for 5 mg, -0.61 for 10 mg, -0.49 for adalimumab and -0.24 for placebo (p < 0.0001).

For DAS-4(ESR) < 2.6:

- In Study A3921032 the proportion of subjects with DAS28-4(ESR) < 2.6 was greater in the active treatment groups 6.72% in the 5 mg (p = 0.0496), 8.80% in the 10 mg (p = 0.0105) and 1.67% in the placebo group.
- In Study A3921044, the proportion of subjects achieving DAS28-4(ESR) was greater in the tofacitinib groups: 7.17% for 5 mg (p < 0.0034)[25], 15.95% for 10 mg (p < 0.0001) compared with 1.55% for placebo.
- In Study A3921064, the proportion of subjects achieving DAS28-4(ESR) < 2.6 at Month 6 was greater in the tofacitinib and adalimumab groups relative to placebo: 6.21% for 5 mg (p = 0.0151), 11.41% for 10 mg (p < 0.0001), 6.74% for adalimumab (p = 0.0091) and 1.09% for placebo.

In Study A3921032, Study A3921044 and Study A3921064 there was no significant difference in efficacy between the two dosing levels[26]. In Study A3921064 there was no significant difference in response between the tofacitinib and adalimumab in efficacy outcome measures. Efficacy was not influenced by prior treatment with TNFα inhibitors. Efficacy was maintained for up to 12 months. The secondary outcome measures were supportive of efficacy.

Efficacy for both dose levels (5 mg bd and 10 mg bd) was demonstrated in monotherapy in Study A3921045:

- For ACR20 response at Month 3, there were 59.75% responders in the 5 mg group, 65.70% in the 10 mg and 26.67% in the placebo group (p < 0.0001).
- For HAQ-DI the change (improvement) from baseline was greater in the tofacitinib groups: LS mean change -0.50 for 5 mg, -0.57 for 10 mg and -0.19 for placebo (p < 0.0001).
- There was no significant difference between tofacitinib and placebo in the proportion of subjects achieving DAS28-4(ESR) < 2.6 at Month 3: 5.60% for 5 mg, 8.73% for 10 mg, and 4.39% for placebo.

[24] Due to step down procedure, the statistical significance for the HAQ-DI endpoint for the tofacitinb 5 mg bd dose could not be declared.
[25] Due to step down procedure, the statistical significance for the DAS28-4(ESR) < 2.6 endpoint for the tofacitinb 5 mg bd dose could not be declared.
[26] There was no statistical comparison between the tofacitinib 5 and 10 mg BD doses. The studies were not powered to detect potential differences between doses.

Efficacy was maintained for up to 6 months. There was no significant difference in response between the 5 mg and 10 mg dose levels in efficacy outcome measures[26]. The secondary outcome measures supported efficacy.

Efficacy was demonstrated as concurrent treatment with traditional DMARDs in Study A3921046:

- For ACR20 response at Month 6, there were 52.73% responders in the 5 mg group, 58.25% in the 10 mg and 31.21% in the placebo group ($p < 0.0001$)
- For HAQ-DI the change (improvement) from baseline was greater in the tofacitinib groups: LS mean change -0.46 for 5 mg, -0.56 for 10 mg and -0.21 for placebo ($p < 0.0001$)
- The proportion of subjects achieving DAS28-4(ESR) < 2.6 at Month 6 was greater in the tofacitinib groups relative to placebo: 9.13% for 5 mg ($p = 0.0038$), 13.33% for 10 mg ($p < 0.0001$), and 2.70% for placebo

Efficacy was maintained for up to 12 months. There was no significant difference in response between the 5 mg and 10 mg dose levels in efficacy outcome measures[26]. Efficacy response was not influenced by the type of background DMARD. The secondary outcome measures supported efficacy.

In A3921024/A3921041 (open-label studies) efficacy (as measured by ACR20, ACR50 and ACR70) appeared to be maintained for up to 3 years.

The outcomes used in the efficacy studies were clinically relevant. The outcomes included symptom scores, measures of disease progression and also measures of wellbeing. The statistical analyses were appropriate.

The populations included in the efficacy studies were consistent with the indication that is being applied for:

> *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. Xeljanz can be used alone or in combination with DMARDS, including methotrexate*

The recommended dosing regimen in the PI document is supported by the efficacy data: *The recommended dosage is 5 mg administered bd. Some patients may benefit from an increase to 10 mg administered bd, based on clinical response*.

Safety

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

In the pivotal efficacy studies, the following safety data were collected:

- adverse events (AEs), serious AEs (SAEs) and AE leading to discontinuation (DAEs)
- AEs of particular interest, including serious infections and CV events
- Laboratory tests, including serum lipids, creatine kinase (CK), creatinine, creatinine clearance, ALT, AST and full blood count (FBC)

Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies provided safety data, as follows:

- AEs, SAEs and DAEs
- Laboratory tests, including serum lipids, CK, creatinine, creatinine clearance, ALT, AST and FBC

Other studies evaluable for safety only

- Study A3921024 is an ongoing, open label, long term, follow-on safety study. It includes subjects that have completed randomised Phase II and Phase III studies. Study A3921041 is also an ongoing long term safety study.
- Study A3921061 is an ongoing, open label, long term safety study in subjects with plaque psoriasis. Limited data listings were provided.
- A3921069 is an ongoing Phase III, randomised, 24 month, double blind, parallel group study comparing tofacitinib with MTX. Some AE data were provided, but were blinded to treatment allocation.

Other studies with limited safety data

- Study A3921009 was a Phase II study of tofacitinib (15 mg and 30 mg bd) as an immunosuppressant in the prevention of graft rejection in renal transplant recipients. There were 61 subjects in the study. Efficacy and safety results were similar to those for tacrolimus. Study A321021 was a follow-on study to Study A3021009. Data listings were provided for Study A3921021 but were blinded for treatment allocation.
- Study A3921030 was a Phase II study of tofacitinib (15 mg bd, followed by 10 mg bd) as an immunosuppressant in the prevention of graft rejection in renal transplant recipients. A total of 322 subjects received treatment. To Month 6, there were higher rates of infection with CP-390,550 than cyclosporine: around 35% subjects compared with 18%. Study A3921050 is an open-label extension study of Study A3921030. Data listings were provided but were blinded to treatment allocation.
- Study A3921043 was a Phase II study of tofacitinib (1 mg, 5 mg or 15 mg bd) in the treatment of Crohn's disease. There was a higher than expected placebo response in this study and although the 5 mg dose appeared to have greater efficacy than placebo, the 1 mg and 15 mg doses did not. The AE profile for tofacitinib was similar to that for placebo.
- Study A3921047 was a Phase II study of tofacitinib (2 mg, 5 mg and 15 mg) compared with placebo in subjects with chronic plaque psoriasis over a 12 week period. A total of 197 subjects were randomised to treatment, 49 in each of the tofacitinib dose groups. Tofacitinib was superior to placebo in the proportions of subjects with PASI75 response. The rates of AEs in the tofacitinib groups were similar to those in the placebo.
- Study A3921063 was a Phase II study of tofacitinib (0.5 mg, 3 mg, 10 mg and 15 mg bd) compared to placebo in the treatment of ulcerative colitis over 8 weeks. A total of 194 subjects received study treatment. Clinical response was recorded in a greater proportion of subjects in the 10 mg and 15 mg groups than in the placebo. The AE rates were similar in the tofacitinib groups to placebo.
- Study A3921073 is an ongoing study of tofacitinib that aims to explore the effect of tofacitinib 10 mg bd on blood and synovial tissue biomarkers in subjects with active RA. AE data were provided but were blinded to treatment allocation.
- Study A3921080 is an ongoing Phase III study comparing tofacitinib with etanercept in the treatment of severe chronic plaque psoriasis. Listings of AEs were provided but were blinded to treatment allocation.

- Study A3921111 is an ongoing Phase III study of treatment withdrawal/re-treatment with tofacitinib in subjects with moderate to severe chronic plaque psoriasis. Listings of AEs were provided but were blinded to treatment allocation.

Patient exposure

The total number of subjects (patient-years) exposed to tofacitinib is stated in the sponsor's *Clinical Summary of Safety* to be 1369 (419.95) in Phase II studies, 3030 (2210.97) in Phase III studies, 3227 (3085.13) in long term extension studies, for a total exposure of 4816 (5716.03) in all of these studies combined. (See AusPAR Attachment 2 for details of exposure in relation to dose).

Adverse events of special interest

Infection

- In Study A3921019 the rates of infection, particularly urinary tract infection, increased with increasing dose. In Study A3921025, Study A3921035, Study A3921039 and Study A3921040, overall the rate of infections increased with increasing tofacitinib dose.
- In Study A3921040, herpes zoster or simplex infections were reported in four subjects in the 10 mg group and three in the 15 mg.
- For Study A3921025, Epstein-Barr virus (EBV) DNA levels reached or exceeded the level of potential concern (> 500 copies/500 ng DNA) in four subjects: two in the 5 mg group, one in the 20 mg once daily group, and one in the 15 mg group.
- In Study A3921032, rates of treated-infection AEs were higher in the 5 mg group (26 treated infections) and the placebo group (24) compared with the 10 mg group (17).
- In Study A3921044, the incidence (95% CI) of serious infections was 4.168 (2.553 to 6.803) per 100 patient years exposure in the 5 mg group, 2.319 (1.207 to 4.457) per 100 patient years in the 10 mg and 3.679 (0.920 to 14.710) per 100 patient years in the placebo.
- In Study A3921045 through Month 6, there was one (0.4%) subject in the 5 mg group with serious infection, four (1.6%) in the 10 mg, one (1.6%) in the placebo/5 mg (during the 5 mg phase) and none in the placebo/10 mg.
- In Study A3921064, serious infections were reported in seven (3.4%) subjects in the 5 mg group, eight (4.0%) in the 10 mg, one (1.8%) in the placebo/5 mg, one (1.9%) in the placebo/10 mg and three (1.5%) in the adalimumab.

Dyslipidaemia

- In Study A3921035, proportion of subjects with dyslipidaemia peaked at the 10 mg dose level, at 8.2%.
- In Study A3921039, there was a higher proportion of subjects in the tofacitinib groups with elevated LDL-C (around 20%), but this was observable from the lowest dose level: 1 mg bd.
- In Study A3921032, during the placebo controlled phase, there was one subject in each of the 5 mg and 10 mg groups with hypertriglyceridaemia. In Study A3921032, there was one subject in the 10 mg group with acute myocardial infarction.
- In Study A3921044 to Month 3, dyslipidaemia was reported in nine (2.8%) subjects in the 5 mg group, 16 (5.1%) in the 10 mg and three (1.9%) in the placebo; myocardial infarction/ischemic heart disease was reported in three subjects in the 10 mg group,

and hypertension was reported in 13 (4.0%) subjects in the 5 mg group, five (1.6%) in the 10 mg and two (1.3%) in the placebo.

- In Study A3921045, to Month 3, dyslipidaemia was reported in eight (3.3%) subjects in the 5 mg group, ten (4.1%) in the 10 mg and one (0.8%) in the placebo. To Month 3, hypertension was reported in two (0.8%) subjects in the 5 mg group, eleven (4.5%) in the 10 mg and three (2.5%) in the placebo; congestive heart failure was reported in eight (3.3%) subjects in the 5 mg group, five (2.0%) in the 10 mg and three (2.5%) in the placebo; and acute myocardial infarction was reported in three (1.2%) subjects in the 5 mg group, ten (4.1%) in the 10 mg and one (0.8%) in the placebo.
- In Study A3921046, to Month 3 dyslipidaemia as an AE was reported in nine (2.9%) subjects in the 5 mg group, twelve (3.8%) in the 10 mg and one (0.6%) in the placebo; hypertension as an AE was reported in five (1.6%) subjects in the 5 mg group, nine (2.8%) in the 10 mg and two (1.3%) in the placebo; acute myocardial infarction was reported in five (1.6%) subjects in the 5 mg group, six (1.9%) in the 10 mg and one (0.6%) in the placebo. From Month 3 to Month 6, acute myocardial infarction was reported in a further one (1.0%) subject in the 5 mg group, and five (1.6%) in the 10 mg, but none in those subjects continuing on placebo.
- In Study A3921064, to Month 3, hypercholesterolaemia was reported in two (1.0%) subjects in the 5 mg group, two (1.0%) in the 10 mg and one (0.5%) in the adalimumab; myocardial infarction was reported in one subject in the 10 mg group and one in the adalimumab; hypertension as an AE was reported in four (2.0%) subjects in the 10 mg group, seven (3.5%) in the 5 mg, two (1.9%) in the placebo and none in the adalimumab.

Treatment comparisons for adverse events of special interest

The sponsor's Integrated Summary of Safety performed comparisons between tofacitinib, placebo and adalimumab and also incorporated literature reports for drugs used to treat RA. Tofacitinib had a similar rate of serious infections, but a higher rate of herpes zoster infections, and resulted in higher serum LDL, in comparison with placebo and other anti-rheumatic drugs.

Postmarketing data

There were no post-marketing data included in the submission.

Evaluator's conclusions on safety

In the pivotal studies, the overall rates of treatment emergent AEs (TEAEs) were similar for the tofacitinib 5 mg and 10 mg dose levels and placebo for up to 3 months of treatment. Beyond 3 months comparisons between tofacitinib and placebo were not possible due to the complicated design of the efficacy studies and the low numbers of subjects in the placebo groups after 3 months. Where incidence rates for TEAEs were provided, the rates of TEAEs were similar for both of the tofacitinib dose levels and for placebo. For example, in Study A3921044 the overall incidence rate (95% CI) for TEAEs was 164.849 (147.014 to 184.848) per 100 patient-years exposure for 5 mg, 171.562 (152.911 to 192.489) per 100 patient-years exposure for 10 mg, and 208.293 (167.755 to 258.628) per 100 patient-years exposure for placebo. The most common TEAEs were infections and abnormal laboratory tests.

In Phase I studies doses up to 100 mg were evaluated, which represents 10 times the higher recommended dose level. Headache and nausea were more common at these very high dose levels. In the Phase II studies, doses of 15 mg bd and above resulted in higher rates of TEAEs than placebo. In the pooled study, Study PMAR-00188, the risk of serious infections increased with dose: the 10 mg bd dose was estimated to have 1.3 to 1.9 times

greater likelihood of serious infections compared to 5 mg bd with the 90% CI excluding ≥ 2.9 relative risk. There was no apparent association between tofacitinib exposure and malignancy risk.

Dyslipidaemia was more common in the tofacitinib treatment groups than placebo. However, possibly due to the follow-up time being too short, there did not appear to be an increased rate of ischaemic heart disease.

Deaths were uncommon and did not appear to be attributable to tofacitinib. The rates of SAE with tofacitinib did not appear to be greater than for either placebo or adalimumab.

The rates of DAE were similar for the two tofacitinib dose levels and for tofacitinib in comparison with placebo and adalimumab. The most common reasons for DAE were infection and elevated ALT or AST.

Mild elevations in ALT and AST were more common in the tofacitinib groups than with placebo or adalimumab. Over 20% of subjects treated with tofacitinib in the studies of 3 Months or longer duration had mild elevations in ALT or AST. However, liver disease and/or marked elevations of ALT or AST were not more common with tofacitinib. Elevation of transaminases, including significant elevation, was more common with concurrent MTX. There was one case of hepatic failure leading to death reported during the development program.

In the pivotal studies there were small but statistically significant increases in serum creatinine and decreases in creatinine clearance (as measure by the Cockroft-Gault method). However, it is not clear whether this represents a decrease in renal function or interference with the active transport of creatinine. There was no increase in reports of acute renal failure in the tofacitinib groups.

There were consistent elevations in HDL, LDL and total cholesterol in the tofacitinib groups. The elevations were in the order of 15% of baseline values. Reports of elevations in CK were also more common in the tofacitinib. These findings may indicate an increase in CV risk.

Neutrophil and platelet counts decreased in a dose dependent manner with tofacitinib. However, neutropenia and thrombocytopenia were uncommon.

First round benefit-risk assessment

First round assessment of benefits

- Tofacitinib in combination with MTX at both the 5 mg and 10 mg bd dose levels results in a clinically and statistically significant improvement in the symptoms of RA. At the 10 mg dose level there was a clinically and statistically significant decrease in disease progression. At both dose levels there was an improvement in wellbeing. These effects were demonstrated in comparison with placebo.
- In monotherapy, tofacitinib at both the 5 mg and 10 mg bd dose levels results in a clinically and statistically significant improvement in the symptoms of RA and an improvement in wellbeing.
- In combination with DMARDs, tofacitinib at both the 5 mg and 10 mg bd dose levels there was a clinically and statistically significant improvement in the symptoms of RA and an improvement in wellbeing.
- Efficacy was maintained for up to 3 years with ongoing treatment.

First round assessment of risks

- The overall rates of TEAEs were similar for tofacitinib and placebo as monotherapy, in combination with MTX, and in combination with DMARDs. As would be expected with an immunomodulatory agent, infections were common. At higher than recommended doses, headache and nausea are common. The likelihood of serious infection increases with tofacitinib dose.
- Dyslipidaemia was more common in the tofacitinib treatment groups than placebo. There were consistent elevations in HDL, LDL and total cholesterol in the tofacitinib groups. The elevations were in the order of 15% of baseline values. Reports of elevations in CK were also more common in the tofacitinib. These findings may indicate an increase in CV risk. However, possibly due to the follow-up time being too short, there did not appear to be an increased rate of ischaemic heart disease.
- Deaths were uncommon and did not appear to be attributable to tofacitinib. The rates of SAE with tofacitinib did not appear to be greater than for either placebo or adalimumab.
- Mild elevations in ALT and AST were more common in the tofacitinib groups than with placebo or adalimumab. Over 20% of subjects treated with tofacitinib in the studies of 3 Months or longer duration had mild elevations in ALT or AST. However, liver disease and/or marked elevations of ALT or AST were not more common with tofacitinib. Elevation of transaminases, including significant elevation, was more common with concurrent MTX. There was one case of hepatic failure leading to death reported during the development program.
- In the pivotal studies there were small, but statistically significant, increases in serum creatinine and decreases in creatinine clearance (as measure by the Cockroft-Gault method). However, it is not clear whether this represents a decrease in renal function or interference with the active transport of creatinine. There was no increase in reports of acute renal failure in the tofacitinib groups.
- Neutrophil and platelet counts decreased in a dose dependent manner with tofacitinib. However, neutropenia and thrombocytopenia were uncommon.

First round assessment of benefit-risk balance

The benefit-risk balance of tofacitinib, given the proposed usage, is favourable.

First round recommendation regarding authorisation

Tofacitinib should be approved for the following indication:

> *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. Xeljanz can be used alone or in combination with DMARDS, including methotrexate.*

Clinical questions

Pharmacokinetics

1. What data does the sponsor have to support PKs in the elderly population? Can the sponsor provide a summary of the data of the available data with regard to clearance of tofacitinib in the older age groupings (that is, age ≥65 years and age ≥75 years)?

2. Does the sponsor have any data with regard to the effects of tofacitinib on glucuronidation of other drugs? Has the sponsor investigated the potential interaction of tofacitinib with paracetamol?
3. Does the sponsor have further data with regard to the mechanism for active renal secretion of tofacitinib? What are the possible consequences of interactions at the level of renal transporters with regard to the PKs of tofacitinib? How does the sponsor plan to manage these risks should tofacitinib be approved for marketing?

Safety

4. What is the mechanism for the increase in serum creatinine and decrease in creatinine clearance observed with long term tofacitinib treatment?
5. Can the sponsor provide further details regarding the case of hepatic failure leading to death reported in Study A3921024/A3921041? Are there any cases potentially fulfilling the three components of Hy's Law that have not been included in the *Integrated Safety Summary - Hepatic*?

Second round evaluation of clinical data submitted in response to questions

With regard the PK of tofacitinib in subjects ≥ 65 years and ≥ 75 years the sponsor provided an updated analysis based on PK data comprising 1710 subjects in total, with 263 patients ≥ 65 years and 21 patients ≥ 75 years. The PK parameters did not appear to be altered in the elderly. The geometric mean ratio (90% CI) for CL/F for elderly subjects/non-elderly subjects was 0.939 (0.923 to 0.957) for subjects ≥ 65 years and 0.971 (0.917 to 1.03) for subjects ≥ 75 years. This indicates no decrease in clearance in the elderly. These conclusions are limited in those subjects ≥ 75 years of age by the small numbers in that subgroup, but the findings for those subjects ≥ 65 years are reassuring.

With regard the effect of tofacitinib on glucuronidation, the sponsor performed an in vitro study (Study CP-6905500) to assess the in vitro inhibition profiles of UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 by tofacitinib in human liver microsomes with and without 2% bovine serum albumin.

In the opinion of the evaluator, based on the information provided, it is unlikely that there are clinically significant interactions at the level of renal drug transporters involving CP-690550.

With regard the mechanism for the increase in serum creatinine and decrease in creatinine clearance observed with long term tofacitinib treatment, the sponsor states that a measured GFR study in RA patients treated with tofacitinib 10 mg bd is ongoing (protocol A3921152). At this stage the sponsor does not have a satisfactory explanation for the phenomenon. However, as the sponsor states, there was no other evidence of nephrotoxicity in the clinical development program and no increase in reports of acute renal failure in the tofacitinib groups. The sponsor has clearly identified nephrotoxicity as a potential risk, as indicated by the need to perform Study A3921152, and in the opinion of the evaluator, it should be included in the Risk Management Plan (RMP).

With regard further details regarding the case of hepatic failure leading to death reported in Study A3921024/A3921041, the sponsor states the subject died one month after terminating study treatment. The hepatic failure was considered to be secondary to sepsis following bacterial (septic) arthritis.

With regard cases potentially fulfilling the three components of Hy's Law that have not been included in the *Integrated Safety Summary - Hepatic*, the sponsor has identified six cases that satisfied the biochemical criteria of Hy's Law. However, the sponsor proposes

alternative explanations for five of these cases. The potential for drug induced liver injury is already included as a 'potential risk' in the RMP.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of tofacitinib in the proposed usage are unchanged from those identified in the *First round assessment of benefits*, above.

Second round assessment of risks

After consideration of the responses to clinical questions, the benefits of tofacitinib in the proposed usage are unchanged from those identified in *First round assessment of risks*, above

Second round assessment of benefit-risk balance

The benefit-risk balance of tofacitinib, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

Tofacitinib should be approved for the following indication:

> *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. Xeljanz can be used alone or in combination with DMARDS, including methotrexate.*

V. Clinical findings third round

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 3 (Round 3 CER).

Introduction

The Third round clinical evaluation was prompted when the sponsor notified the TGA of a negative opinion of the EMA Committee for Medicinal Products for Human Use (CHMP), recommending against market authorisation for tofacitinib on the grounds of safety concerns. 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 grounds for refusal by the CHMP[27] were:

> Ground 1: The evidence for an effect of tofacitinib on prevention of structural damage progression in the proposed patient population (that is, 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 5 mg bd is insufficient. The magnitude of effect in this population cannot be sufficiently

[27] For full details of the EMA considerations of the application in the EU, see EMA/CHMP/425279/2013 Committee for Medicinal Products for Human Use (CHMP). Assessment report. Xeljanz tofacitinib. Procedure No. EMEA/H/C/002542/0000 25 July 2013. [European Public Assessment Report (EPAR) for tofacitinib]

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 CV 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.

The clinical evaluator's assessment of the sponsor responses to the CHMP grounds for refusal is provided under *Comments on the response to the CHMP from the sponsor,* below.

The proposed indication at this time was:

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. Xeljanz can be used alone or in combination with DMARDS, including methotrexate.

Contents of the clinical dossier

The additional data provided for evaluation by the TGA comprised:

- Two clinical trials with PD 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 negative opinion.

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.

Pharmacodynamics

Studies providing PD data

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

Primary PD effects

Study A3921073 was a multicentre, Phase II, randomised, double blind, parallel group PD study in subjects with RA. 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. The study treatments were: tofacitinib 10 mg bd or placebo. Treatment duration was for 4 weeks. The outcome measures included arthroscopy, serum mRNA, and serum pro-inflammatory cytokine levels.

Secondary PD 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. Healthy volunteers were used as a reference group. Subjects with RA were administered tofacitinib 10 mg bd for 6 weeks.

Evaluator's conclusions on PDs

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.

Efficacy

Studies providing efficacy data

Efficacy in comparison with MTX

- Study A3921069 was a multicentre, randomised, double blind, parallel group comparator controlled trial of tofacitinib 5 mg and 10 mg bd in comparison with MTX in MTX-naïve subjects with RA. The study treatments were: tofacitinib 5 mg bd; tofacitinib 10 mg bd; or 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.

  The primary efficacy outcome measures were: structure preservation as measured by mTSS at Month 6, and signs and symptoms as measured by ACR70 at Month 6.

Other efficacy studies

- Study A3921129 was a multicentre, randomised, double blind, parallel group, placebo controlled study evaluating immune response following administration of influenza and pneumococcal vaccines to RA patients receiving tofacitinib or placebo with and without background MTX treatment. The study treatments were tofacitinib 10 mg bd or placebo.

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

- Vaccine Sub-study 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 had been evaluated in the First round clinical evaluation report (CER). The new data related to a vaccine sub-study. Eligible subjects had been participating in Study A3921024 and had been receiving tofacitinib 10 mg bd for at least 3 months continuously.

The treatment groups were: continuous tofacitinib 10 mg bd, or tofacitinib withdrawn for 2 weeks then resumed either as monotherapy or on background MTX.

Both groups were stratified by MTX co-medication. Influenza and pneumococcal vaccines were administered on Day 8 after tofacitinib was withdrawn. The outcome measure was immunogenicity, as measured by antibody response to pneumococcal and influenza antigens.

Evaluator's conclusions on 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 group 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 bd. 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.

Safety

Studies providing safety data

Safety data were available from all the studies discussed above under *Pharmacodynamics* and *Efficacy*. There were no additional pivotal or non-pivotal safety studies.

Patient exposure

- In Study A3921130 there were 36 subjects with RA exposed to tofacitinib 10 mg bd for 6 weeks.
- In Study A3921073 there were 15 subjects exposed to tofacitinib 10 mg bd for 4 weeks.
- In Study A3921069 there were 371 subjects treated with tofacitinib 5 mg and 395 treated 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 Sub-study A3921024 there were 99 subjects exposed to tofacitinib 10 mg bd continuously, and 99 subjects who had tofacitinib interrupted for 2 weeks. Treatment during the Sub-study was for up to 80 days.

Evaluator's conclusions on 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. 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 group. 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 group.

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 (that is, immunosuppression) and is common to DMARDs, both non-biological and biological.

Third round benefit-risk assessment

Third round assessment of benefits

In addition to the benefits identified in Round 1 and Round 2 (see above and 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.

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 bd. 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. 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 CV 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 (that is, 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 (bDMARDs).

Evaluator's assessment of sponsor responses to the CHMP comments

The following provides a summary of the sponsor's responses to concerns raised by the EMA CHMP (see *Introduction* above) and the clinical evaluator's review of these responses. See AusPAR Attachment 3 for full details.

Sponsor response to CHMP comment: 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 clinical evaluator, this argument is valid and is consistent with the data and the indication sought by the sponsor.

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

In the opinion of the clinical 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 minimising 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.

Sponsor response to CHMP comment: 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 III 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) 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 CV 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 CV 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.

Sponsor response to CHMP comment: 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 randomised controlled trials. 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 (that is, no alternative treatments were available) the risks may be acceptable.

Third round assessment of benefit-risk balance

The benefit-risk balance of tofacitinib, given the proposed usage, is favourable. The proposed usage is understood by the evaluator to be the patient population that has no alternative treatment available (that is, has failed treatment with both biological and non-biological DMARDs, or where these agents are contraindicated)[28].

Third round recommendation regarding authorisation

The clinical evaluator is unable to recommend approval of the submission with the indication as proposed:

> *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. 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 emphasise 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 recognise and manage the safety risks associated with this treatment.

[28] The sponsor subsequently clarified to the TGA that it had not changed its position in the Australian application that a second line indication is the most appropriate for Xeljanz, based on the scope of the development program and the demonstration of a favourable benefit:risk in RA patients in second line therapy.

The clinical evaluator would be able to recommend approval of the submission with the following amended indication:

> *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. Xeljanz can be used alone or in combination with DMARDS, including methotrexate. Therapy with Xeljanz should be initiated and monitored by a specialist rheumatologist.*

Round 3 clinical questions

Safety

1. Were there any treatment emergent ECG abnormalities in Study A3921069?
2. Have the safety data from Vaccine Sub-study A3921024 previously been provided for evaluation in the TGA Round 1 or 2 evaluation phases?
3. Has Study A3921152 reached completion and are the data available for evaluation?
4. One case of potential drug induced liver injury (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?

Delegate's initial overview: Clinical aspects

Background

The following Overview, dated 29 August 2013, was prepared by the Delegate after review of the First, Second and Third Round CERs, in anticipation of submitting this application for advice from the Advisory Committee on Prescription Medicines (ACPM) in October 2013. The request for ACPM advice was subsequently deferred pending a fourth round clinical evaluation.

Only the clinical efficacy and safety aspects of the Delegate's initial Overview are shown below (see Delegate's final Overview under *Overall conclusion and risk/benefit analysis,* below, for details of additional aspects considered for this application, including nonclinical, chemistry and RMP).

The indication proposed by the sponsor at the time this Overview was prepared was as follows:

> *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. Xeljanz can be used alone or in combination with non-biologic DMARDS, including methotrexate.*
>
> *Therapy with Xeljanz should be initiated and monitored by a specialist physician with expertise in the management of rheumatoid arthritis.*

The proposed recommended dose was 5 mg bd, which may be increased to 10 mg bd based on clinical response.

Clinical data

The clinical evaluator had reviewed the submitted data, which included:

- 27 clinical pharmacology studies (20 PK, 7 PD studies, including 2 additional studies for the Third round evaluation)
- 2 population PK analyses
- 6 pivotal efficacy/safety studies (one was submitted for the Third round evaluation following EMA questions on efficacy and safety)
- 2 vaccine studies
- 5 dose finding studies
- 2 long term follow-on studies
- an Integrated Summary of Efficacy, Integrated Summary of Safety (including an updated version submitted for additional evaluation, 10 analyses of combined data)

After evaluating the clinical data, the concerns raised by the EMA and the sponsor's response to those concerns, the clinical evaluator recommended refusing the currently proposed indication (Third round CER (see AusPAR Attachment 3)), highlighting the following issues:

- the sponsor's proposed indication does not adequately reflect the arguments made by the sponsor in response to the CHMP refusal of marketing approval;
- the proposed indication does not sufficiently emphasise that the sponsor proposes tofacitinib to be a third line agent[29];
- that healthcare professionals knowledgeable in the management of RA would be required to recognise and manage the safety risks associated with this treatment;
- the following clinical concerns:
  - serious infections
  - malignancies
  - dyslipidaemia
  - creatinine rise on tofacitinib
  - liver function abnormalities
  - haematological parameter changes (neutrophils, lymphocytes).

The evaluator recommended approval of the following amended indication:

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

Efficacy

Five dose finding Phase II studies for tofacitinib were conducted, as monotherapy (2) or in combination with MTX (2) or adalimumab (1). As monotherapy, daily doses of 2 to 60 mg daily (in divided doses) were compared with placebo with a plateau of effect observed (ARC20) at the 15 mg bd dose. In combination with MTX, bd doses ranging from 1-15 mg versus placebo were assessed, with a range of endpoint effects observed from 5-20 mg bd,

[29] The sponsor subsequently clarified that it had not changed its position in the Australian application that a second line indication is the most appropriate for Xeljanz, based on the scope of the development program and the demonstration of a favourable benefit:risk in RA patients in second line therapy.

with ARC20 peaking at 10 mg bd. In combination with adalimumab, doses from 1-15 mg bd were assessed against placebo. The ARC20 peaked at 10 mg bd dose. A comparison of the effect of tofacitinib dose on Japanese versus Caucasian subjects all receiving MTX demonstrated no significant difference in effect between the two populations. The doses of 5 and 10 mg were used for subsequent Phase III studies.

Table 4: Summary of the six pivotal efficacy trials

Study	Design and control type; background treatment	Duration of Treatment	Test Product Dose regimen	Numbers for each arm
A3921032	Phase III, randomised, double-blind, placebo controlled, parallel group study of tofacitinib as add-on to MTX; TNF inhibitor IR on background MTX	6 months: first 3 months placebo controlled, further 3 months following reassignment to active treatment	5 mg tofacitinib bd; 10 mg tofacitinib bd; Placebo, then 5 mg tofacitinib bd after 3 months; Placebo, then 10 mg tofacitinib bd after 3 months	133: 5 mg 134: 10 mg, 66: placebo/5 mg 66: placebo/10 mg
A3921044	Phase III, randomised, double-blind, placebo-controlled, parallel group study of tofacitinib as add-on to MTX; MTX IR on background MTX	12 months (3 to 6 months of placebo) If after 3 months, no response** in placebo then active treatment, otherwise advanced after 6 months	5 mg tofacitinib bd; 10 mg tofacitinib bd; Placebo/5 mg tofacitinib bd; Placebo/10 mg tofacitinib bd	321: 5 mg group 316: 10 mg 81: placebo/5 mg 79: placebo/10 mg

Study	Design and control type; background treatment	Duration of Treatment	Test Product Dose regimen	Numbers for each arm
A3921064	Phase III randomised, double blind, placebo controlled, parallel group study to compare tofacitinib or adalimumab with placebo in subjects on stable MTX dose; MTX IR on background MTX	12 months (3 to 6 months of placebo) If after 3 months, no response** in placebo then active treatment, otherwise advanced after 6 months	5 mg tofacitinib bd; 10 mg tofacitinib bd; Placebo/5 mg tofacitinib bd; Placebo/10 mg tofacitinib bd; Adalimumab 40 mg SC every 2 weeks	204: 5 mg group 201: 10 mg 56: placebo/5 mg 52 placebo/10 mg 204: adalimumab.
A3921045	Phase III, randomised, 6-month, double blind, placebo controlled, parallel group trial of tofacitinib as monotherapy in subjects with inadequate response to DMARD*; DMARD IR* None	6 months: first 3 months placebo controlled, further 3 months following reassignment to active treatment	5 mg tofacitinib bd; 10 mg tofacitinib bd; Placebo/5 mg tofacitinib bd; Placebo/10 mg tofacitinib bd	243: 5 mg group 245: 10 mg 61: placebo/5 mg 61: placebo/10 mg
A3921046	Phase III randomised, double-blind, placebo-controlled, parallel group study of two doses of tofacitinib and concurrent treatment with DMARDs†; DMARD* IR on background DMARD/s	12 months (3 to 6 months of placebo) If after 3 months, no response** in placebo then active treatment, otherwise advanced after 6 months	5 mg tofacitinib bd plus tDMARD; 10 mg tofacitinib bd plus tDMARD; Placebo/5 mg tofacitinib bd plus tDMARD; Placebo/10 mg tofacitinib bd plus tDMARD	315: 5 mg group 318: 10 mg group 79: placebo/5 mg 80: placebo/10 mg

Study	Design and control type; background treatment	Duration of Treatment	Test Product Dose regimen	Numbers for each arm
A3921069	Phase III randomised, double-blind, study of two doses of tofacitinib versus MTX; MTX naïve None	24 months (interim 12-month results reported only)	5 mg tofacitinib bd; 10 mg tofacitinib bd; MTX minimum 10 mg up to 20 mg/week as tolerated	37: 15 mg tofacitinib bd 395: 10 mg tofacitinib bd 185: MTX

*Subject must have an inadequate response to at least one DMARD (traditional or biologic) due to lack of efficacy or toxicity. No requirement for prior or concomitant treatment with MTX. All DMARDs except antimalarials, traditional and biological, including MTX were to be discontinued with an adequate washout period prior to study treatment
** If there was not at least a 20% improvement in both the tender/painful and swollen joint counts as reported in the study database, the patient was considered a nonresponder.
†Subject must have been on at ≥1 background tDMARD and remain on that throughout the study.

Table 5 shows the absolute numbers who completed the treatment in each study with the percentage of those randomised to the treatment arm in brackets.

Table 5: Absolute numbers who completed the treatment (percentage of those randomised to the treatment arm)

Study	No completed 5 mg	No completed 10 mg	No completed placebo/ 5 mg	No completed placebo/ 10 mg	No. completed
1032	107 (80.5)	103 (76.9)	53 (80.3)	48 (72.7)	N/A
1044	250 (77.9)	265 (83.1)	64 (79)	64 (81)	N/A
1064	150 (70)	159 (78.6)	47 (83.9)	39 (75)	adalimumab 164 (79.4)
1045	232 (95.1)	218 (89)	54 (88.5)	51 (83.6)	N/A
1046	261 (82.1)	252 (79.2)	71 (89.9)	67 (83.8)	N/A
1069	307 (82.1%)	328 (82.4%)	N/A	N/A	MTX 134 (72.0%)

Figures show number of patients (% of randomised) completed.

Pivotal studies

The pivotal analysis comprised efficacy data from six Phase III trials (A3921032, A3921044, A3921064, A3921045, A3921046, and A3921069). The first five were randomised, double blind, paired placebo controlled, parallel group efficacy and safety studies, and all examined the effect of either 5 mg bd or 10 mg bd against paired placebo control. The sixth trial (submitted for evaluation after CHMP refusal for marketing

authorisation) was a randomised trial without paired placebo controls and compared tofacitinib 5 mg bd or 10 mg bd with MTX. The first two trials (1032, 1044) compared tofacitinib in combination with MTX with paired placebo groups; the third trial (1064) incorporated an additional comparator arm of MTX plus adalimumab. Trial 1045 examined tofacitinib as monotherapy in those who had progressed on at least one DMARD (traditional or biological) and the final study (1046) examined tofacitinib in combination with at least one tDMARD versus paired placebo.

Four key inclusion criteria were standard for all the pivotal studies: to have RA with evidence of active RA with ≥ 4 out of 7 ACR criteria, active disease at screening and baseline (both minimum of 6 tender/painful joints on motion (of 68 assessed) and minimum of 6 swollen joints (of 66 assessed)[30], active disease with either ESR > 28 mm/h or CRP > 7mg/L, and Class I, II or III of ACR 1991 Revised Criteria for Global Functional Status in RA.

Further inclusion criteria included an acceptable minimum wash-out period (at least 4 weeks) for all previous DMARDS (traditional and biological), biological response modifiers, immunosuppressants and corticosteroids was determined and varied according to the agent, unless these were specifically being compared with tofacitinib.

Key exclusion criteria were estimated GFR < 40 mL/min[31] or AST/ALT > 1.5 x upper limit of normal (ULN), current infection or recent infection requiring parenteral therapy or any disseminated herpes family viral infections; any significant lymphatic or lymphoproliferative disorder, malignancy (other than adequately excised non-melanoma skin cancers or cervical cancer), any prior treatment with non-B lymphocyte-selective lymphocyte depleting agents/therapies or total lymphoid irradiation; any human immunodeficiency virus (HIV), hepatitis B or C infection.

The patient ages and gender included were consistent with the population affected by RA: there were more than 80% women and the ages ranged from 18-86 years.

Primary efficacy endpoints were:

- ACR20 at time points specified according to trial duration: 3 Months for 6 month studies, 6 Months for 12-24 month studies
- Physical function as measured by the HAQ-DI change from baseline at Month 3
- Incidence of DAS28-4 (ESR) < 2.6 at time points specified according to trial duration: 3 Months for 6 month studies, 6 Months for 12-24 month studies
- For 1044, an additional endpoint of structure preservation measured by mTSS change from baseline at month 6 was included.

Secondary efficacy endpoints included:

Additional time point measures of ACR20, DAS28-4 (ESR) and HAQ-DI; 3 Month and beyond time points for ACR50/70, DAS28-3 (CRP), and the quality of life measures: (Short-Form) SF-36 health survey, EuroQol EQ-5D, MOSS-SS, FACIT-fatigue scale, healthcare resource utilization (HCRU), work limitation questionnaire (WLQ). In trial 1044, mTSS was an extra secondary efficacy endpoint.

The efficacy and safety analyses were performed on the full analysis set, which included any subject randomised who received at least one dose of the study drug or placebo. The sample size calculations were performed at the specified time point of primary efficacy outcome measures separately, using a step-down procedure: for ACR20 analysis, > 90% power assuming a difference in response rates of at least 20% (assuming placebo

[30] Except in Study A3921046 where active disease at both screening and baseline was defined by having both: 4 tender/painful joints on motion (out of 68 joints assessed) and 4 swollen joints (out of 66 joints assessed).
[31] GFR < 60 mL/min for Study A3921069

response of 30%); for analysis of HAQ-DI, > 90% power for differences > 0.3 assuming a standard deviation (SD) of 0.75; for analysis of DAS28-4 (ESR) < 2.6, assuming a difference in response rates of at least 15% (placebo response set at 10%). For Study 1044, where the mTSS score was measured, the analysis was based on a power of 90% and an α level of 0.05, and assumed a median (SD) change of 1.4 (3.4) for the placebo group and 0.6 (1.8) for the 10 mg group. Imputation was applied to missing values due to a patient dropping from the study for any reason (such as lack of efficacy or AE) by setting the ACR value to non-responsive (that is, baseline observation visit carried forward) from that visit onward.

Safety outcome measures were AEs, laboratory tests, vital signs and ECGs.

Pivotal studies in combination with methotrexate (1032, 1044, 1064)

Both 1032 and 1044 compared 6 months and 12 months respectively of tofacitinib with placebo in subjects with RA already on MTX. Study 1064 had the same design as 1044 but with the inclusion of an additional arm of adalimumab 40 mg every two weeks. All trials required ongoing treatment with a stable dose of MTX (minimum 4 months' duration, stable dose of 7.5-25 mg weekly in 6 weeks prior to first study dose; MTX doses below 15 mg were allowed where intolerance, toxicity or local indication prevented higher MTX dose). All included a wide age range: 20-84 years (Study 1032), 18-82 years (Study 1044) and 18-83 years (Study 1064).

In Study 1032, participants were required to have previous use of at least one TNF inhibiting biologic agent, discontinued because inadequately effective and/or not tolerated (11.5% patients completing the study); 30.8% had previously taken other tDMARDs. In this 6 month study, 399 patients were randomised into 4 groups (2:2:1:1) to receive either 5 mg bd or 10 mg bd tofacitinib paired with placebo control groups switched to 5 mg bd or 10 mg bd tofacitinib after 3 months. The lowest completion rate was 79% (see Table below).

There were subjects in the tofacitinib 5 mg group, in the tofacitinib 10 mg and in the MTX still receiving treatment at Month 12.

Table 6: Normal approximation to ACR20 response rates at Month 3 (FAS, NRI, difference from placebo) (Study A3921032)

Treatment	N	n	%	Difference From Placebo			
				Difference	95% CI for Difference		P-Value
					Lower	Upper	
CP-690,550 5 mg BID	132	55	41.67	17.23	6.06	28.41	0.0024
CP-690,550 10 mg BID	133	64	48.12	23.69	12.45	34.92	<0.0001
Placebo	131	32	24.43				

Source: Table 14.2.3.1.1

Abbreviations: ACR20 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, NRI = nonresponder imputation

Table 7: Summary of LS mean changes from baseline in HAQ-DI at Month 3 (FAS, NRI, differences from placebo) (Study A3921032)

Treatment	N	LS Mean	Differences From Placebo			
			Difference	95% CI for Difference		P-value
				Lower	Upper	
CP-690,550 5 mg BID	117	-0.43	-0.25	-0.36	-0.15	<0.0001
CP-690,550 10 mg BID	125	-0.46	-0.28	-0.38	-0.17	<0.0001
Placebo	118	-0.18				

Source: Table 14.2.13.3.1

Abbreviations: BID = twice daily, CI = confidence interval, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire - Disability Index, LS mean = least squares mean, N = number of patients, NRI = nonresponder imputation

Table 8: Summary of patients achieving DAS28-4(ESR) < 2.6 at Month 3 (FAS, NRI, comparisons to placebo) (Study A3921032)

Treatment	N	n	%	Comparison to Placebo			
				Difference	95% CI for Difference		P-value
					Lower	Upper	
CP-690,550 5 mg BID	119	8	6.72	5.05	0.00	10.10	0.0496
CP-690,550 10 mg BID	125	11	8.80	7.13	1.66	12.60	0.0105
Placebo	120	2	1.67				

Source: Table 14.2.15.10.1

Abbreviations: BID = twice daily, CI = confidence interval, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, NRI = nonresponder imputation

Active treatment with either the 5 mg or 10 mg dose resulted in a significant improvement in all 3 endpoint measures. There was no significant difference in efficacy between the two dose levels.

In a subset analysis, there was no significant difference in efficacy for those with prior TNFα inhibitor therapy.

Other secondary efficacy outcomes were the maintenance of a greater response in the ACR20, HAQ-DI, DAS28-4 in the active treatment groups compared with placebo at 6 months. In addition, response rates of the remaining secondary outcomes measured were greater in the active treatment groups compared with placebo and this was maintained to 6 months, with the exception of the SF-36 which demonstrated improvement at 3 months alone, and the WLQ which demonstrated significant improvement for some of the measures such as mental/interpersonal demands and time management but not for physical demands.

Study 1044 was a 2 year study (data up to 12 months were provided) with 3-6 months of placebo then reallocation if not a responder [a nonresponder was defined if there was not at least a 20% improvement in both the tender/painful and swollen joint counts]. Additional inclusion criteria were presence of active RA with joint erosions or positive Rheumatoid Factor (RF+) or antibodies to cyclic citrullinated peptide (anti-CCP) or evidence of ≥ 3 distinct joint erosions on PA hand or wrist radiographs. The dose regimen and groups were the same as Study 1032 except for study duration, with placebo groups only receiving tofacitinib after 3 months if no response was demonstrated at that time, otherwise all the placebo groups were switched to tofacitinib.

800 patients, aged 18-82, were randomised 4:4:1:1. 797 received treatment with completion rates consistent across the different groups (see Table above).

Table 9: Normal approximation to ACR20 response rates at Month 6 (FAS, NRI, differences from placebo, 1-Year analysis) (Study A3921044)

Treatment	N	n	%	Difference From Placebo			
				Difference of %s	95% CI for Difference		p-value
					Lower	Upper	
CP-690,550 5 mg BID	309	159	51.46	26.13	17.28	34.97	<0.0001
CP-690,550 10 mg BID	309	191	61.81	36.48	27.73	45.23	<0.0001
Placebo	154	39	25.32				

Source: Table 14.2.1.1
Abbreviations: ACR20=American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures, CI=confidence interval, FAS=Full Analysis Set, N=number of patients, n=number of patients meeting prespecified criteria, NRI=nonresponder imputation, BID=twice daily

Table 10: Summary of LS mean changes from baseline in Modified Total Sharp Scores (mTSS) at Month 6 (FAS, LEP, differences from placebo, 1-Year Analysis) (Study A3921044)

Treatment	N	LS Mean	Differences From Placebo			
			LS Mean Difference	95% CI for Difference		p-value
				Lower	Upper	
CP-690,550 5 mg BID	277	0.12	-0.34	-0.73	0.04	0.0792
CP-690,550 10 mg BID	290	0.06	-0.40	-0.79	-0.02	0.0376
Placebo	139	0.47				

Source: Table 14.2.15.1.6
Abbreviations: BID=twice daily, CI=confidence interval, FAS=Full Analysis Set, LS=least squares, N=number of patients, LEP=linear extrapolation
mTSS (Sharp/van der Heijde method) defined in Section 9.5.3.1.
If patients did not have any valid postbaseline radiographs, they were not included in this summary.

Table 11: Summary of LS mean changes from baseline in HAQ-DI at Month 3 (FAS, differences from placebo, 1-Year Analysis) (Study A3921044)

Treatment	N	LS Mean	Differences From Placebo			
			LS Mean Difference	95% CI for Difference		p-value
				Lower	Upper	
CP-690,550 5 mg BID	294	-0.40	-0.25	-0.34	-0.16	<0.0001
CP-690,550 10 mg BID	300	-0.54	-0.40	-0.49	-0.31	<0.0001
Placebo	146	-0.15				

Source: Table 14.2.11.5
Abbreviations: BID=twice daily, CI=confidence interval, FAS=Full Analysis Set, HAQ-DI=Health Assessment Questionnaire - Disability Index, LS=least squares, N=number of patients
Nominal p-values are presented for information; however, due to the predefined stepdown procedure (see Section 9.7.3.1), significance at the 5% level can only be claimed for the CP-690,550 10 mg BID group compared to placebo.

Table 12: Summary (%) of patients achieving DAS28-4(ESR) < 2.6 at Month 6 (FAS, NRI, comparisons to placebo, 1-Year Analysis) (Study A3921044)

Treatment	N	n	%	Comparison to Placebo			
				Difference	95% CI for Difference		p-value
					Lower	Upper	
CP-690,550 5 mg BID	265	19	7.17	5.61	1.85	9.38	0.0034
CP-690,550 10 mg BID	257	41	15.95	14.40	9.44	19.36	<0.0001
Placebo	129	2	1.55				

Source: Table 14.2.13.19
Abbreviations: BID=twice daily, DAS=Disease Activity Score, ESR=erythrocyte sedimentation rate, FAS=Full Analysis Set, N=number of patients, n=number of patients meeting prespecified criteria, CI=confidence interval, NRI= nonresponder imputation.
Nominal p-values are presented for information; however, due to the predefined stepdown procedure (see Section 9.7.3.1), significance at the 5% level can only be claimed for the CP-690,550 10 mg BID group compared to placebo.

Table 13: Normal approximation to rates of patients (%) with no progression in mTSS at Months 6 and 12 (FAS, LEP, comparisons to placebo, 1-Year Analysis) (Study A3921044)

Time point/ Treatment	N	n	%	Difference From Placebo			
				Difference in %	95% CI for Difference		p-value
					Lower	Upper	
Month 6							
CP-690,550 5 mg BID	277	246	88.81	11.11	3.25	18.96	0.0055
CP-690,550 10 mg BID	290	252	86.90	9.19	1.26	17.13	0.0230
Placebo	139	108	77.70				
Month 12							
CP-690,550 5 mg BID	286	246	86.01	11.91	3.59	20.23	0.0050
CP-690,550 10 mg BID	295	255	86.44	12.33	4.07	20.60	0.0034
Placebo	139	103	74.10				

Source: Table 14.2.15.4.1
Abbreviations: BID=twice daily, CI=confidence interval, FAS=Full Analysis Set, N=number of patients, n=number of patients meeting prespecified criteria, LEP=linear extrapolation, mTSS=modified Total Sharp Score
mTSS (Sharp/van der Heijde method) defined in Section 9.5.3.1.
No progression in mTSS defined as change from Baseline ≤0.5 units.

In Study 1044, active treatment with either the 5 mg or 10 mg dose resulted in a significant improvement in all 4 endpoint measures. The additional endpoint of mTSS was reported as significantly improved at 6 months in those receiving 10 mg but not 5 mg, suggesting slowed progression of joint destruction over this time.

There was no significant difference between the two dose levels in terms of efficacy outcome measures[32].

Other secondary efficacy outcomes were the maintenance of a greater response in the ACR20, HAQ-DI, DAS28-4 in the active treatment groups compared with placebo at 12 months. At 12 months, the mTSS measurements were greater for both the 5 and 10 mg groups compared with placebo ($p < 0.01$). In addition, response rates for the remaining secondary outcomes measured were greater in the active treatment groups compared with placebo at 6 months and this was maintained to 12 months for ACR50 and 70. A greater response at Month 3 lasting through until Month 12 in the active treatment groups for DAS-28-4 (ESR), DAS28-3 (CRP), and EQ-5D was reported. For the remainder of the secondary efficacy outcomes, there were a range of responses: fatigue measurements

[32] Sponsor clarification: There was no statistical comparison between the tofacitinib 5 and 10 mg bd doses. The studies were not powered to detect potential differences between doses.

were reported to have improved in the active treatment arms, and at 3 and 6 months the SF-36 responses indicated an improvement. The WLQ and MOSS-SS (sleep disturbance scale) responses indicated no effect of active treatment at Month 6.

Study 1064 was a one year study designed to compare the efficacy of tofacitinib 5 mg and 10 mg bd compared with placebo in patients already on MTX. A further arm of adalimumab in patients on MTX was added, however, it was not a superiority study nor non-inferiority study so tofacitinib was not compared to adalimumab. Consistent with the aims, exclusion criteria included failure of a TNFα inhibitor, any prior treatment with adalimumab, and to permit safe randomisation to the adalimumab arm, those with Class III or IV heart failure (New York Heart Association) or any other contraindication to adalimumab were excluded. Primary efficacy endpoints were the same as for Studies 1032 and 1044, with the addition of an mTSS measurement.

717 subjects on stable doses of methotrexate were randomised 4:4:4:1:1 to receive bd doses of 5 mg or 10 mg tofacitinib, 40 mg adalimumab SC every fortnight or paired placebo (with tofacitinib introduced at 3 months if no response [a nonresponder was defined if there was not at least a 20% improvement in both the tender/painful and swollen joint counts], or for all on placebo at 6 months). Prior DMARD use was similar across the groups, and previous TNFα inhibitor treatment had been used in 5.9% of the 5 mg group, 7% of the 10 mg group, 7.1% of placebo/5 mg group, 9.6% of placebo/10 mg group and 7.8% in the adalimumab group.

Table 14: Normal approximation to ACR20 response Rates at Month 6 (FAS, NRI, difference from placebo) (Study A3921064)

				Difference From Placebo			
					95% CI for Difference		
Treatment	N	n	%	Difference	Lower	Upper	P-Value
CP-690,550 5 mg BID	196	101	51.53	23.22	12.16	34.29	<0.0001
CP-690,550 10 mg BID	196	103	52.55	24.24	13.18	35.31	<0.0001
Adalimumab 40 mg SC q 2 weeks	199	94	47.24	18.93	7.90	29.96	0.0007
Placebo	106	30	28.30	-			

Source: Table 14.2.1.1

Abbreviations: ACR20 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures; BID = twice daily; CI = confidence interval; FAS = full analysis set; LS mean = least squares mean; N = number of patients; n = number of patients meeting prespecified criteria; NRI = nonresponder imputation; q = every; SC = subcutaneous.

Table 15: Summary of LS mean changes from baseline in HAQ-DI at Month 3 (FAS, differences from placebo) (Study A3921064)

			Differences From Placebo			
			LS Mean	95% CI for Difference		
Treatment	N	LS Mean	Difference	Lower	Upper	P-value
CP-690,550 5 mg BID	188	-0.55	-0.31	-0.43	-0.19	<0.0001
CP-690,550 10 mg BID	185	-0.61	-0.38	-0.50	-0.25	<0.0001
Adalimumab 40 mg SC q 2 weeks	190	-0.49	-0.25	-0.37	-0.13	<0.0001
Placebo	98	-0.24	-			

Source: Table 14.2.11.5

Abbreviations: BID = twice daily; CI = confidence interval; FAS = full analysis set; HAQ-DI = Health Assessment Questionnaire - Disability Index; LS = least squares; N = number of patients; q = every; SC = subcutaneous.

Table 16: Summary of patients achieving DAS28-4(ESR) < 2.6 at Month 6 (FAS, NRI, comparisons to placebo) (Study A3921064)

Treatment	N	n	%	Difference from Comparator			
				Difference	95% CI for Difference		P-value
					Lower	Upper	
CP-690,550 5 mg BID	177	11	6.21	5.12	0.98	9.26	0.0151
CP-690,550 10 mg BID	176	22	12.50	11.41	6.08	16.73	<0.0001
Adalimumab 40 mg SC	178	12	6.74	5.65	1.40	9.90	0.0091
Placebo	92	1	1.09	-			

Source: Table 14.2.13.11.1
Abbreviations: BID = twice daily; CI = confidence interval; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; FAS = full analysis set; N = number of patients; n = number of patients meeting prespecified criteria; NRI = nonresponder imputation; SC = subcutaneous.

Study 1064 investigated the effect of combined treatment with tofacitinib and MTX, and adalimumab (at the recommended dose of 40 mg given every two weeks) and MTX significantly improved all measurements of the 3 primary efficacy endpoints compared with the paired placebo groups.

There was no significant difference in efficacy between the 5 mg and 10 mg dose levels, or between tofacitinib and adalimumab.

Other secondary efficacy outcomes were the maintenance of a greater response in the ACR20, HAQ-DI, DAS28-4 in the active treatment groups compared with placebo at 3 months and maintained through to 12 months. The ACR 50 and 70 response rates were greater in the active treatment groups at 3 months and this response increased through to 12 months. There was a reduction in DAS28-3 (CRP) from 3 months to the 6 Month point, and an improvement in fatigue levels and EQ-5D for the same period for the tofacitinib and adalimumab groups compared with placebo. The SF-36 at Month 6 was improved for tofacitinib compared with placebo but not adalimumab to the same extent. Significant improvement in sleep compared with placebo was noted for the tofacitinib groups, with some improvement noted for adalimumab at 6 months. The WLQ indicated no change with active treatment apart from some improvement in time and management demands for the 10 mg tofacitinib group.

Pivotal study as monotherapy

Study 1045 was a 6 month study of tofacitinib as monotherapy compared with paired placebo groups in those where RA had progressed on any tDMARD or bDMARD. The exclusion criteria were similar to the above trials, with no requirement for previous or concomitant treatment with methotrexate, and all must have had an adequate washout period of any discontinued therapy prior to commencement.

Primary and secondary efficacy endpoints were as for Study 1032. The determinants for each endpoint were the same as for Study 1032, and hypothesis tests were performed in the same manner.

611 subjects were randomised 4:4:1:1 to receive 5 mg or 10 mg tofacitinib bd, with paired placebos switching to 5 mg or 10 mg after 3 months; 610 commenced and 555 completed the study treatment. Prior to enrolment, 84.9% had taken MTX, 66.4% had taken a tDMARD other than MTX, and 6.7% had used a bDMARD. Concomitant antimalarial agents were taken by 18.4% in the 5 mg group, 16.7% in the 10 mg group, 13.1% in the placebo/5 mg group and 11.5% in the placebo/10 mg group.

Efficacy tables:

Table 17: Normal approximation to ACR20 response rates at Month 3 (FAS, NRI, difference from placebo) (Study A3921045)

Treatment	N	n	%	Difference From Placebo			
				Difference	95% CI for Difference		P-Value
					Lower	Upper	
CP-690,550 5 mg BID	241	144	59.75	33.08	23.04	43.13	<0.0001
CP-690,550 10 mg BID	242	159	65.70	39.04	29.12	48.95	<0.0001
Placebo	120	32	26.67				

Source: Table 14.2.1.1

Abbreviations: ACR20 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, NRI = nonresponder imputation

Table 18: Summary of LS mean changes from baseline in HAQ-DI at Month 3 (FAS, differences from placebo) (Study A3921045)

Treatment	N	LS Mean	Differences From Placebo			
			Difference	95% CI for Difference		P-value
				Lower	Upper	
CP-690,550 5 mg BID	237	-0.50	-0.31	-0.43	-0.20	<0.0001
CP-690,550 10 mg BID	227	-0.57	-0.38	-0.50	-0.27	<0.0001
Placebo	109	-0.19	Not applicable			

Source: Table 14.2.1.2

Abbreviations: BID = twice daily, CI = confidence interval, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire - Disability Index, LS = least squares, N = number of subjects

Table 19: Summary of patients achieving DAS28-4(ESR) < 2.6 at Month 3 (FAS, NRI, comparisons to placebo) (Study A3921045)

Treatment	N	n	%	Comparison to Placebo			
				Difference	95% CI for Difference		P-value
					Lower	Upper	
CP-690,550 5 mg BID	232	13	5.60	1.22	-3.57	6.00	0.6179
CP-690,550 10 mg BID	229	20	8.73	4.35	-0.90	9.59	0.1042
Placebo	114	5	4.39	Not applicable			

Source: Table 14.2.15.10.1

Abbreviations: BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, NRI= nonresponder imputation, CI = confidence interval

Of the primary efficacy endpoints, only ACR20 and HAQ-DI were significantly improved by active treatment compared with placebo, while DAS28-4 (ESR) levels did not change significantly. Other secondary efficacy outcomes were the maintenance of the significantly improved response in the ACR20 and HAQ-DI at 6 Months, and for sleep and SF-36 responses at Month 3. Non-significant improvements in DAS28-4 (ESR), DAS28-3 (CRP), EQ-5D, fatigue scales in the active treatment groups compared with placebo at 3 months were maintained through to 6 months. No difference was seen in the WLQ responses at Month 3.

Pivotal study as concurrent treatment with DMARDs

Study 1046

This 12 month study of tofacitinib in combination with a DMARD (traditional) compared with paired placebo groups (who likewise were on a background DMARD) in those with RA, which included those with moderate to severe disease. Additional criteria included having at least 4 tender painful joints on motion (out of 68 joints assessed) and at least 4 swollen joints (out of 66 assessed), and the subject must be on a tDMARD and remain on that for the duration of the study. Traditional DMARDs were permitted, but others could

be included after discussion with the sponsor. The DMARDs used included MTX, sulfasalazine, leflunomide, hydroxychloroquine sulphate, injectable gold and penicillamine. Efficacy outcomes were the same as Trial 1032, except that primary efficacy outcomes were measured at Month 6.

795 subjects were randomised 4:4:1:1 to receive twice daily doses of 5 mg or 10 mg with paired placebo groups switching to twice daily doses of 5 mg or 10 mg at 3 months if response was not achieved [nonresponder defined if there was not at least a 20% improvement in both the tender/painful and swollen joint counts], and all remaining in the placebo groups switching at 6 months. The age range was 18-86 years, the mean age was 52 years, and 14% were over 65 years of age. MTX was the most common DMARD prior to screening followed by leflunomide, and TNFa inhibitors had been used taken prior to screening by 23 (7.3%) subjects in the 5 mg group, 19 (6.0%) in the 10 mg group, five (6.3%) in the placebo/5 mg and five (6.3%) in the placebo/10 mg group.

Table 20: Normal approximation to ACR20 response rates at Month 6 (FAS, NRI, comparisons to placebo) (Study A3921046)

Treatment	N	n	%	Difference from Comparator			
				Difference	95% CI for Difference		P-Value
					Lower	Upper	
CP-690,550 5 mg BID	311	164	52.73	21.52	12.39	30.65	<0.0001
CP-690,550 10 mg BID	309	180	58.25	27.04	17.94	36.13	<0.0001
Placebo	157	49	31.21				

Source: Table 14.2.1.1
Abbreviations: ACR20 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, CI = confidence interval, FAS = full analysis set, LS mean = least squares mean, N = number of patients, n = number of patients meeting prespecified criteria, NRI = nonresponder imputation

Table 21: Summary of LS mean changes from baseline in HAQ-DI at Month 3 (FAS, differences from placebo) (Study A3921046)

Treatment	N	LS Mean	Differences From Placebo			
			LS Mean Difference	95% CI for Difference		P-value
				Lower	Upper	
CP-690,550 5 mg BID	292	-0.46	-0.26	-0.35	-0.16	<0.0001
CP-690,550 10 mg BID	292	-0.56	-0.35	-0.44	-0.26	<0.0001
Placebo	147	-0.21	Not Applicable			

Source: Table 14.2.11.1.7
Abbreviations: BID = twice daily, CI = confidence interval, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire - Disability Index, LS = least squares, N = number of patients

Table 22: Summary of patients achieving DAS28-4(ESR) < 2.6 at Month 6 (FAS, NRI, comparisons to placebo) (Study A3921046)

Treatment	N	n	%	Difference from Comparator			
				Difference	95% CI for Difference		P-value
					Lower	Upper	
CP-690,550 5 mg BID	263	24	9.13	6.42	2.07	10.77	0.0038
CP-690,550 10 mg BID	270	36	13.33	10.63	5.80	15.45	<0.0001
Placebo	148	4	2.70	Not applicable			

Source: Table 14.2.13.4.1
Abbreviations: BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, NRI= nonresponder imputation, CI = confidence interval

For primary efficacy outcomes, the active treatment resulted in a significantly improved ACR20, HAQ-DI and DAS28-4 compared with placebo.

There was no significant difference in efficacy between the 5 mg and 10 mg dose levels[33].

Other secondary efficacy outcomes included maintenance of the improvement in ACR20, HAQ-DI and DAS28-4 with active treatment at 12 months. Improved ACR50 and 70 response rates, DAS28-3 (CRP) reductions, and improved fatigue scores were seen from Months 3-12, while other quality of life ratings such as the EQ-5D improved at 3 and 6 Months and sleep improved at 3 Months but was not maintained at 6 Months. There was no significant difference as measured by WLQ. This study was affected by the low numbers in the placebo groups.

Pivotal study as comparator with MTX

Study 1069 was a multicentre, two year, randomised, double blind, parallel group comparator controlled trial of tofacitinib 5 mg and 10 mg bd in comparison with MTX in subjects with RA. The study was submitted for evaluation by the TGA following concerns expressed by the CHMP about safety and efficacy, and had not been evaluated prior to registration by the FDA. Additional inclusion and exclusion criteria were included compared with the rest of the efficacy trials listed here, and are included in the following list:

Notable inclusion criteria were:

- 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 immunoglobulin M (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 (≥ 4 in Study 1046).
- The patient must have had one at least of the following criteria at screening: ESR > 28 mm/h or CRP > 7 mg/L.
- No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB).

Notable exclusion criteria were:

- 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;
- GFR < 60 mL/min (previously < 40 mL/min for other trials);
- 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.

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%.

[33] Sponsor clarification: There was no statistical comparison between the tofacitinib 5 and 10 mg bd doses. The studies were not powered to detect potential differences between doses.

The primary efficacy outcome measures were structure preservation as measured by mTSS at Month 6, and signs and symptoms as measured by ACR70 at Month 6.

The secondary efficacy outcome measures aimed to identify joint structure preservation, signs and symptomatic control, physical function and patient reported outcomes. Structure preservation was determined by assessing actual and mTSS change from baseline at Months 12 and 24, actual and any change in two individual components of mTSS: erosion and joint space narrowing (JSN) scores at Months 6, 12, and 24, non-progression of mTSS (mTSS change ≤ 0.5) and rate of "no new erosions" (erosion score ≤ 0.5). Differing levels of DAS28-3 (CRP) and DAS-28-4 were used, and durability of ACR20/50/70 responses was used to determine biochemical and clinical responses respectively. Tools for measuring physical function and quality of life were those used in the other trials.

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

958 patients were randomised 2:2:1 and 952 received either twice daily tofacitinib doses of 5 mg or 10 mg or MTX 10 mg/week titrated up to 20 mg/week over 8 weeks according to tolerance. All other DMARDs were discontinued with an appropriate wash out period. The age characteristics were very similar across all three arms, with a range of 18-83 years, mean ages of 48-50, and 10-11% of subjects were over the age of 65. The treatment groups were similar with respect to previous DMARD use.

Table 23: Summary of LS mean changes from baseline in Modified Total Sharp Scores (mTSS) at Month 6 (FAS, LEP, 1-Year Analysis) (Study A3921069)

			Differences From MTX			
			LS Mean	95% CI for Difference		
Treatment	N	LS Mean	Difference	Lower	Upper	p-value
Tofacitinib 5 mg BID	346	0.18	-0.66	-1.03	-0.28	0.0006
Tofacitinib 10 mg BID	369	0.04	-0.81	-1.18	-0.44	<0.0001
Methotrexate	166	0.84				

If patients did not have any valid postbaseline radiographs, they were not included in this summary.
Abbreviations: BID=twice daily, CI=confidence interval, FAS=full analysis set, LS=least squares, N=number of patients, LEP=linear extrapolation, MTX=methotrexate

Table 24: Normal approximation to ACR70 response rates at Month 6 (FAS, NRI, Differences from MTX, 1-Year Analysis) (Study A3921069)

				Difference From MTX			
				Difference	95% CI for Difference		
Treatment	N	n	%	of %	Lower	Upper	p-value
Tofacitinib 5 mg BID	369	94	25.47	13.51	7.05	19.97	<0.0001
Tofacitinib 10 mg BID	393	148	37.66	25.70	18.99	32.40	<0.0001
Methotrexate	184	22	11.96				

Abbreviations: ACR70=American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures, CI=confidence interval, FAS=full analysis set, N=number of patients, n=number of patients meeting prespecified criteria, NRI=nonresponder imputation, BID=twice daily, MTX=methotrexate

Table 25: Number (%) of patients with ACR70 response sustained at least 6 months (FAS, No imputation, 1-Year Analysis) (Study A3921069)

	N	n (%)	Exact 95% CI for %
Tofacitinib 5 mg BID	371	61 (16.44)	(12.82, 20.61)
Tofacitinib 10 mg BID	395	97 (24.56)	(20.39, 29.11)
Methotrexate	186	11 (5.91)	(2.99, 10.34)

Table 26: Normal approximation of rates (%) of patients with no progression in mTSS at Months 6 and 12 (FAS, LEP, comparisons to MTX, 1-Year Analysis) (Study A3921069)

Time point/ Treatment	N	n	%	Difference From MTX			
				Difference in %	95% CI for Difference		p-value
					Lower	Upper	
Month 6							
Tofacitinib 5 mg BID	346	289	83.53	13.04	5.08	21.00	0.0013
Tofacitinib 10 mg BID	369	331	89.70	19.21	11.61	26.82	<0.0001
Methotrexate	166	117	70.48				
Month 12							
Tofacitinib 5 mg BID	345	280	81.16	16.45	8.16	24.73	<0.0001
Tofacitinib 10 mg BID	370	321	86.76	22.05	14.07	30.02	<0.0001
Methotrexate	170	110	64.71				

Source: Table 14.2.15.4.1
If patient did not have any valid postbaseline radiographs, they were not included in this summary.
No progression in mTSS defined as change from Baseline ≤0.5 units.
Abbreviations: BID=twice daily, CI=confidence interval, FAS=full analysis set, N=number of patients, n=number of patients meeting prespecified criteria, LEP=linear extrapolation, mTSS=modified Total Sharp Score, MTX=methotrexate

For the primary efficacy endpoints, 5 mg bd or 10 mg bd tofacitinib was significantly better than MTX in improving ACR70 scores at 6 Months (for 5 mg: 95% CI 7.05 to 19.97, $p < 0.0001$ and for 10 mg: 95% CI 18.99 to 32.40, $p < 0.00001$). The reductions in mTSS scores relative to methotrexate at 6 Months were significantly different in favour of tofacitinib 5 mg (95% CI -1.03 to -0.28, $p < 0.0006$) and 10 mg (95% CI -1.18 to -0.44, $p < 0.0001$. A subset analysis demonstrated a trend to a smaller effect for twice daily tofacitinib 5 mg where prior DMARD treatment.

The secondary endpoints generally supported a greater magnitude and duration of effect of both dose levels of tofacitinib compared with MTX. Specifically, statistically significant increases in ACR20, 50 and 70 were seen from Month 2-12 for both dose levels. The number with no progression as determined by mTSS at 12 Months was significantly greater for tofacitinib 5 mg (81.16%) and 10 mg (86.76%) compared with MTX (64.71%), $p < 0.0001$. No data was offered for any other structural assessments beyond 12 months, despite this being one of the secondary efficacy endpoints. An improvement in inflammatory markers was seen with both doses levels of tofacitinib compared with methotrexate but this was not significant.

No statistics for comparison between the efficacies of the different dose levels were presented.

Other efficacy studies

Long term follow-on studies

A3921024/A3921041 were long term tolerability, safety and efficacy studies conducted in subjects who had completed Studies A3921019, A3921025, A3921032, A3921035, A3921044, A3921045, A3921046, A3921064, A3921069, A3921073, A3921109, A3921039, and A3921040. The efficacy outcome measures were ACR20, ACR50, ACR70, HAQ-DI score and DAS28-4(ESR).

3227 subjects were included: 1321 treated with tofacitinib 5 mg bd and 1906 treated with 10 mg bd. Of these, 2019 were also on background DMARDs and 1208 were on tofacitinib monotherapy. 83% were women, the age range was 18 to 86 years (mean age of 53), and 16.8% were 65 years or older. At the date of cut-off there were 1022 (77%) subjects ongoing in the 5 mg group and 1768 (92.8%) in the 10 mg. There were 970 subjects treated for more than 12 months, 659 for more than 24 months and 62 for more than 36 months. Efficacy (as measured by ACR20, ACR50 and ACR70), reduction in HAQ-DI and

DAS28-4 appeared to be maintained for up to 3 years. There were no data for comparison of the dose levels, nor efficacy as monotherapy compared with combined treatment.

Vaccine studies

Study A3921129

This was a multicentre, randomised, double blind, parallel group, placebo controlled study evaluating immune response following administration of influenza and pneumococcal vaccines to RA patients receiving tofacitinib or placebo with and without background MTX treatment. No other DMARD or parenteral glucocorticoid use was permitted, but continuation of previously stable doses of NSAIDs and/or oral corticosteroids was allowed.

The study inclusion and exclusion criteria were similar to those for Study 1032. Exclusion criteria included: evidence of active or latent or inadequately treated TB; 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 outcomes were humoral response to pneumococcal and influenza vaccines and the safety outcomes were AEs, vital signs, clinical laboratory tests and ECGs.

223 subjects were randomised according to MTX use with 112 receiving tofacitinib 10 mg bd and 111 receiving placebo. The age range was 23-82 years, with 77% being women and the groups were similar in their demographic characteristics. On day 29, both groups received the pneumococcal and influenza vaccines.

The response rates to pneumococcal vaccination (all serotypes) were significantly decreased in those who had taken 28 days of tofacitinib: 45.1% versus 68.4% for placebo (difference -23.3%, 95% CI -36.6 to -9.6), which was partially modified where there was concomitant MTX. There were similar response rates to the influenza vaccine.

Vaccine sub-study A3921024

This was a vaccine sub-study carried out within the long term efficacy, safety and tolerability Study A3921024 described above. Within the groups taking continuous tofacitinib 10 mg bd for ≥ 3 months, 100 were randomised to continue the dose at that level and 99 had tofacitinib withdrawn for 2 weeks (Days 1-14) and then resumed at the same dose. The groups were stratified according to MTX use, which was maintained throughout. Both groups received a pneumococcal vaccine and influenza vaccine on Day 8. The rates of humoral response to the pneumococcal vaccine were 75% in the continuous and 84.6% in the interrupted group: treatment difference (95% CI) -9.6% (-24.0 to 4.7%). Similar response rates were reported for the influenza vaccine which was not statistically significant difference in the response rates to either vaccine was observed.

Of note, the response rates to the pneumococcal study of the group from A3921024 who had taken tofacitinib 10 mg bd for a minimum of 3 months prior to vaccination was markedly higher than the response rates of either the group who had received tofacitinib for a total of 28 days prior to immunisation or no tofacitinib at all in the second study (75% versus 45.1% versus 68.4%). This difference between the two study response rates has not been commented upon, but makes interpretation of the results somewhat difficult. It would imply that 28 days' treatment has a greater impact in terms of decreasing response rates to immunisations than longer durations. It is not clear whether the same vaccines were used between the two studies.

Summary and discussion of efficacy

The studies conducted were adequately powered to detect the differences being examined in each study. They included adequate number of patients, although in some studies, the number completing placebo or control treatments were low, with those dropping out being classified thereafter as non-responders, which would potentially bias towards finding an effect in favour of the study drug. The age ranges were adequate, but overall there were only 10-17% over the age of 65 years randomised, which, given the increased prevalence of RA in this age group, means they are under-represented. The completion rates were greater than 75% across all the studies.

Tofacitinib been shown to be effective as a single agent, and in combination with MTX or other DMARDs in decreasing the clinical signs and symptoms for patients with moderate to severe RA, at both 5 mg and 10 mg bd doses. It has been shown to be similar in effect to the TNFα inhibitor, adalimumab, and both were significantly more effective than placebo. Extension studies suggest an ongoing benefit for patients on both dose levels in terms of managing their signs and symptoms.

Five trials compared the dose levels and found no significant difference between the efficacies of the 5 mg bd and the 10 mg bd doses[34]. However, the 5 mg dose did not have a significant effect on limiting structural damage at 6 Months in one study (1044), and when used as a single agent after DMARD failure or intolerance, there was no significant alteration of the ESR compared with placebo raising a concern as to whether the underlying inflammatory process was being significantly limited at this dose.

There were some methodological limitations in the studies addressing structural damage. Furthermore, for mTSS score assessments to be valid in assessing an effect on structural damage to joints, improvements are required to be shown after 12 months of therapy and maintained at 2 years, compared with baseline. This was a secondary endpoint for Study 1069, but no data on mTSS beyond 12 months were presented, and the duration of Study 1044 did not permit this; thus it has not been adequately established that tofacitinib has any significant effect on limiting structural joint damage. Studies 1044 and 1069 are not directly comparable: no benefit in controlling structural damage of the 5 mg dose compared with placebo was demonstrated by change in mTSS in Study 1044, while a significant improvement was found in those on the 10 mg dose level in that study. In the Study 1069 of tofacitinib versus MTX, there was no control placebo arm and therefore while the effects observed on reducing the structural damage at 6 and 12 Months of 5 and 10 mg doses were significantly better than the MTX, it is difficult to draw conclusions about the absolute benefits of tofacitinib.

However, when used in combination with other DMARDs, the addition of 5 mg bd tofacitinib significantly improved the clinical signs and symptoms and inflammatory markers compared with placebo. When single agent tofacitinib was compared with single agent MTX, both doses levels of tofacitinib were significantly more efficacious than MTX alone. These data suggest that tofacitinib is most effective when used in combination rather than as a single agent, although there is still some benefit in improving clinical signs and symptoms when used as a single agent. Completion rates were highest of all the studies where tofacitinib used as monotherapy rather than in combination, suggesting tolerability is better as a single agent.

Limitations of methodology

Overall, there were insufficient numbers to permit satisfactory demonstration of any effect of prior TNFα inhibitor treatment on response rates to tofacitinib. In particular, the study

[34] Sponsor clarification: There was no statistical comparison between the tofacitinib 5 and 10 mg bd doses. The studies were not powered to detect potential differences between doses.

of tofacitinib as a single agent (Study 1045) included only 16.2% patients who had prior TNFα inhibitor therapy; therefore this is not an adequate trial as third line therapy. As there was no direct comparison with a TNFα inhibitor to demonstrate superiority, or non-inferiority, only inferences of the relative efficacy of tofacitinib compared with adalimumab can be made, and its role as a second line therapy has not been adequately demonstrated.

In the comparison between tofacitinib and MTX (Study 1069), the duration of therapy on MTX, especially in those newly diagnosed where the dose was gradually escalated, may have been insufficient to determine the effectiveness of this therapy.

Patients with severe renal failure or moderate to severe hepatic failure were excluded from five of the Phase III trials and those with moderate renal failure were excluded from the remaining, most recently conducted trial (1069). Given the PK effects observed in the earlier phase trials, there is no safety data to support use of tofacitinib in those with these conditions.

The number of subjects over the age of 65 years randomised to receive treatment ranged from 10-17%. This may be due to failing screening, especially with the increased likelihood of comorbidities and laboratory test abnormalities (such as impaired renal function) but as a consequence, there is relatively limited safety and efficacy data available for this population. With the numbers enrolled, it would not be possible to perform a subset analysis.

Safety

The total number of subjects (patient-years) exposed to tofacitinib is 1369 (419.95) in Phase II studies, 3030 (2210.97) in Phase III studies, 3227 (3085.13) in long term extension studies, for a total exposure of 4816 (5716.03) in all of these studies combined. In the open label long term safety study, 1321 have been treated with tofacitinib 5 mg bd and 1906 treated with 10 mg bd. There were 970 subjects treated for more than 12 months, 659 for more than 24 months and 62 for more than 36 months.

Adverse events including serious adverse events

Data regarding the safety of tofacitinib was drawn from a range of early dose-finding studies and non-pivotal efficacy studies, pivotal efficacy studies and other ongoing studies evaluable for safety only. Other studies using tofacitinib in diseases other than RA, for example as an immunosuppressant in renal transplant recipients, Crohn's disease and ulcerative colitis, were included. In five out of eight such studies, the AE rates were reported as similar to the placebo, but were blinded to treatment allocation. Consistent with its proposed mode of action, tofacitinib is associated with an increased risk of bacterial and viral infections. Its use was associated with an increased incidence of infections compared with tacrolimus but not compared with cyclosporine. In ulcerative colitis, patients receiving 10 or 15 mg bd had an increased clinical response and the same incidence of AEs as, the placebo arm.

In the pivotal studies, after the switch to active treatment at either 3 or 6 months, it is difficult to attribute AEs rates to a particular treatment. A trend for more infections, particularly upper respiratory infections emerged and laboratory test abnormalities emerged, particularly for those trials of longer duration.

In the Phase I studies, doses up to 100 mg were used and were associated with an increased incidence of headache and nausea. Additional AEs were herpes zoster and diarrhoea.

In Phase II studies, the doses ranged from 1 mg to 30 mg bd. The risk of headache, nausea, leucopenia and infection increased with increasing dose, and hyperlipidemia was identified in 11.3% patients on the 10 mg bd dose regimen.

In the open label follow-on studies, the most common TEAEs were: nasopharyngitis (10%), upper respiratory tract infection (7.3%), urinary tract infection (4.6%), hypertension (4.2%), bronchitis (4.5%), back pain (3.3%), influenza (3.3%), herpes zoster (4.1%), headache (3.7%), diarrhoea (3.4%), sinusitis (2.8%), and RA (2.4%).

The combined data from four Phase II studies (Study A3921025, Study A3921035, Study A3921039 and Study A3921040) and two long term, open-label extension studies (Study A3921024 and Study A3921041) was examined to determine long term risk for serious infections and malignancy. In these studies 4.66% of subjects developed serious infections (incidence rate 2.39 per 100 patient-years) and 2.64% developed a malignancy (incidence rate 1.36 per 100 patient-years). The risk of serious infections increased with dose: the 10 mg bd dose was estimated to have 1.3 to 1.9 times greater likelihood of serious infections compared to 5 mg bd, with the 90% CI excluding ≥ 2.9 relative risk. There was no apparent association between tofacitinib exposure and malignancy risk.

In the pivotal studies which utilised the doses being sought in this application, one in three of the trials where tofacitinib was added to MTX (1064) yielded an increased rate of serious infections in the tofacitinib groups compared with placebo or adalimumab; in the other two trials (1032, 1044), the rates did not vary between the treatment arms. Where tofacitinib was used as monotherapy, there were 11 serious infections: 3 in the 5 mg group and 8 in the 10 mg group. For those receiving 5 mg or 10 mg doses of tofacitinib bd compared with MTX (Trial 1069), there were more AEs, (including SAEs) in the MTX arm than either of the tofacitinib arms. The SAEs in the tofacitinib arms were predominantly infections, including pneumonia, herpes zoster, bone tuberculosis, chronic bronchitis, Dengue fever and typhoid.

Gastrointestinal perforations occurred in 10 patients receiving 10 mg bd dose, but none was seen in the Phase III studies or long term extension studies at the 5 mg dose level. Gastrointestinal perforation is a well-recognised risk of patients with RA, especially with the use of NSAIDs and corticosteroids, and all patients affected were using either or both of these medications. It is unclear whether JAK inhibition by tofacitinib is involved in increasing this risk further. The EMA identified that this risk profile was consistent with other biological agents such as etanercept and tocilizumab.

Further safety information for the Third round clinical evaluation was submitted, including this additional safety data. In the updated Integrated Summary of Safety, there appeared to be an increased risk of lymphoma, compared to the background US population, which was dose related. The sponsor estimates the overall incidence rate for lymphoma was 0.070 events per 100 patient-years (95% CI: 0.034 to 0.148), and the standardised incidence ratio for lymphoma in the tofacitinib RA program was 2.36 (95% CI: 0.95 to 4.86), as compared with the Surveillance Epidemiology and End Result (SEER) United States database. The incidence rate for lymphoma increased with dose: incidence rate (95% CI) 0.046 (0.006 to 0.33) per 100 patient-years for 5 mg bd compared to 0.081 (0.020 to 0.33) per 100 patient-years for 10 mg bd.

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.

The sponsor highlighted that the incidence rates of AEs of special interest (infection, malignancy and CV) 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.

Deaths were uncommon and did not appear clearly attributable to tofacitinib. The mortality rate (95% CI) in the open label studies for the 5 mg dose was 0.760 (0.473 to 1.223) per 100 patient-years, and for the 10 mg dose the rate was 0.340 (0.110 to 1.055) per 100 patient-years.

Table 27: Incidence rates (events/100 patient-years) for Safety Events of Interest, tofacitinib 5 mg bd and 10 mg bd cohorts, in the ongoing open label populations study. Data taken from updated Integrated Summary of Safety.

Parameter	**5 mg BID Cohort** N = 1955 Exposure = 2174 pt-yr Incidence Rate (95% CI) [number of pts with event]	**10 mg BID Cohort** N = 1846 Exposure = 2460 pt-yr Incidence Rate (95% CI) [number of pts with event]
Serious Adverse Events	10.16 (8.87, 11.63) [210]	11.13 (9.86, 12.57) [261]
Adverse Events Resulting in Discontinuation	7.87 (6.77, 9.14) [170]	9.18 (8.05, 10.47) [223]
Mortality (deaths within 30 days of last dose)	0.28 (0.12, 0.61) [6]	0.20 (0.09, 0.49) [5]
Serious Infections	2.73 (2.11, 3.52) [59]	3.56 (2.88, 4.39) [87]
Tuberculosis	0.092 (0.023, 0.37) [2]	0.37 (0.19, 0.70) [9]
Opportunistic Infections*	0.46 (0.25, 0.86) [10]	0.65 (0.40, 1.06) [16]
Herpes Zoster	4.00 (3.23, 4.95) [84]	4.75 (3.95, 5.71) [113]
Malignancies (excl. NMSC)	0.83 (0.52, 1.32) [18]	0.94 (0.62, 1.41) [23]
Lymphoproliferative Disorders/Lymphoma	0.046 (0.006, 0.33) [1]	0.081 (0.020, 0.33) [2]
Composite MACE (adjudicated)†	0.50 (0.22, 1.11) [6]	0.36 (0.18, 0.72) [8]

Subject exposure time is the sum of the tofacitinib exposure from the index study and the tofacitinib exposure from the LTE study. Some events may have occurred post end of treatment, these events were counted in the numerator and subjects' full tofacitinib treatment exposure was included in denominator.
BID=twice daily; CI=confidence interval, N=number of patients; NMSC = nonmelanoma skin cancer, MACE = major adverse cardiovascular event; N=number of patients; P2P3LTE=Phase 2, Phase 3, and long term extension studies; pt-yr=patient years; pts=patients
* Opportunistic infections including tuberculosis
†Composite MACE is from the Phase 3/LTE cohort only (5 mg: N=1530, exposure=1203 pt-yr; 10 mg: N=1512, exposure=2215 pt-yr) as the adjudication of cardiovascular events began in the beginning of Phase 3 program, and did not include patients in the Phase 2 studies.
Source: (19 April 2012), P2P3LTE Tables 485.3.1, 485.3.2, 485.3.3, 485.3.4, 485.3.5, 485.3.6, 485.3.7, 485.3.8, 485.3.9, 485.3.10.

Laboratory marker abnormalities

Liver function

Liver function test abnormalities were consistently reported in those on tofacitinib across all the pivotal trials, especially those of longer duration, and were predominantly a mild increase in AST and/or ALT. These abnormalities appeared to increase with increasing dose of tofacitinib and concomitant MTX or other DMARDs. In the Phase III studies, cases of hepatic enzymes increases were commonly reported: in background DMARD studies, in the first 3 months, there were 28 reports of ALT increased and 20 of AST increased with tofacitinib, 1 with adalimumab and 11 with placebo.

Liver function related AEs were higher in the tofacitinib 5 mg and 10 mg dose groups (1.8% and 2.5%, respectively) compared with the placebo group (0.5%) and the adalimumab group (1.5%) from 3 to 6 months. After 6 months of treatment, more patients had hepatic AEs in the tofacitinib 5 mg and the 10 mg dose groups (2.4% and 3.3%, respectively) than in the adalimumab group (0.5%). Thus, the potential hepatic toxicity of tofacitinib appears to be greater than for adalimumab, including the rates of severe liver enzyme abnormalities (> 3 x ULN).

However, there was no increase in the rates of serious liver test abnormalities overall for those receiving tofacitinib versus other agents or placebo. There was one death due to hepatic failure in a patient who had received 10 mg bd tofacitinib; despite discontinuation of the tofacitinib; the liver function tests worsened after 2-3 months with the pattern of liver injury potentially drug-related. The sponsor reports that it was difficult to determine whether this was a drug induced liver injury or autoimmune hepatitis as there was some improvement with corticosteroids and azathioprine.

In the pivotal studies, those receiving tofacitinib had increases in serum creatinine (greater with 10 mg tofacitinib compared with the 5 mg dose level) and a decrease in creatinine clearance, although the significance of this is uncertain. More cases of acute renal failure were seen in the tofacitinib treatment arms (10 cases) than in the placebo or adalimumab arms (2 cases). The EMA reported much higher absolute numbers of patients who developed acute renal failure when receiving tofacitinib (19 patients for 5 mg; 22 patients for 10 mg), compared with placebo (2 patients) in the Phase III/long term extension studies. With the trial design to switch to tofacitinib after either 3 or 6 months, most patients will have received tofacitinib therefore it is difficult to interpret absolute numbers from long term extension studies and compare with those who received a placebo for a short period of time. In the response to this Overview, the sponsor was asked to provide further information regarding the collection of such data for those who discontinued tofacitinib, particularly in the long term extension studies.

Dyslipidaemia

The evidence for dose related dyslipidaemia is more compelling, with reports of increased LDL-C and triglycerides. Elevated LDL-C (around 20%) was observed in the early studies with doses as low as 1 mg, and appeared to be dose-dependent. In the pivotal efficacy studies either in combination with MTX or as a single agent, dyslipidaemia was reported in more patients receiving tofacitinib than placebo and the incidence peaked at the 10 mg dose. A secondary PD study (submitted in response to the CHMP questions regarding safety) has suggested that this is in part due to the reversal of the catabolic cholesterol ester seen in those with RA. However, the observed increase and absolute levels on tofacitinib were not only higher than the placebo group but also higher than those on adalimumab plus MTX arm of Study 1064, suggesting this may be more than just an effect of reversing the underlying disease process. In one study, the addition of atorvastatin in the group receiving tofacitinib reversed the dyslipidaemia. It is suggested in the PI that these are monitored and managed accordingly.

Haematological

The haematological parameters affected most commonly were platelet and neutrophil counts but neutropenia and thrombocytopenia were relatively uncommon.

The EMA had identified and expressed concern regarding the decline in lymphocytes following an initial increase in those on tofacitinib compared with placebo. This decline persisted with duration of treatment with tofacitinib, unlike adalimumab where the initial increase in lymphocyte counts persisted through the 12 months of that study. Furthermore, the rate of moderate to severe lymphopenia (58.6% and 31.1% in the 5 and the 10 mg dose groups, respectively) in long term extension studies raises concerns about the long term effects on the immune system and risk of infection. The sponsor reports 0.31% patients in this long term safety group receiving 5 or 10 mg of tofacitinib had confirmed absolute lymphocyte counts > 0.5×10^9 cells/L.

An additional safety study was provided by the sponsor for evaluation which appeared to show the B lymphocyte counts returning to normal rapidly after ceasing treatment, and NK cell counts recovering within a week, but this was only after 28 days' treatment. A six week animal study (rats) revealed delayed recovery after 6 weeks' treatment with tofacitinib.

Drug interactions

There is significant potential for drug interactions, specifically those inducing or inhibiting CYP3A4, with ketoconazole doubling the AUC by 103%, and rifampicin decreasing it by with fluconazole affecting both renal excretion and hepatic metabolism. Taken together, and given the relatively narrow therapeutic window (deaths observed in monkeys when AUC was 3 times the therapeutic level), concomitant medications need to be monitored carefully.

Overall discussion: risk/benefit analysis

Efficacy

The efficacy of tofacitinib at 5 mg bd has been established as combination therapy with other DMARDs, and as a single agent in reducing the clinical signs and symptoms in those with moderate to severe RA. According to the EMA Guidelines adopted for use in Australia for assessing RA drugs, the window for detection of any benefit in reducing structural damage is 12 months compared with baseline, and to demonstrate duration of such benefit requires comparison between baseline and after 2 years of therapy. Thus, there is no proven reduction in the progression of structural damage, unlike other DMARDs available. Furthermore, while the ACR20, 50 and 70 were significantly improved after 12 months of treatment with MTX, neither the 5 mg nor 10 mg dose levels demonstrated a significant effect on serum inflammatory markers, which raises some uncertainty about whether the underlying inflammatory process is being controlled. There are no direct studies available for comparison with the effects of the TNFα inhibitors to determine whether tofacitinib is superior or equivalent to these agents.

There were insufficient numbers of patients in Study 1046 receiving tofacitinib in combination with a tDMARD other than MTX to determine the relative efficacies of combining tofacitinib with a non-MTX tDMARD compared with placebo. The numbers who had received prior treatment with a TNFα inhibitor were also low, making it difficult to assess combination with a non-MTX tDMARD as either a second or third line therapy.

Overall, there were insufficient numbers to permit satisfactory analysis of any effect of prior TNFα inhibitor treatment on response rates to tofacitinib.

Although there appeared to be a trend towards an increased efficacy in some studies with the 10 mg dose, in the 5 Phase III placebo controlled studies, there was no significant difference in efficacy demonstrated between the 5 mg and 10 mg dose levels[35]. No dose level efficacy comparison was provided for the comparator trial with MTX. There was no study presented where the dose was escalated from 5 mg to 10 mg to obtain additional clinical benefit. As no statistically significant increase in efficacy has been demonstrated between the two dose levels, there is no evidence to support escalating the dose from 5 mg to 10 mg for clinical effect as the sponsor has sought in the indication. The indication is reliant upon a presumed increased responsiveness at the 10 mg dose level in those who have failed 5 mg bd.

Safety

There is however, a significant increase in toxicity with increasing dose with more AEs, especially infections, risk of malignancy, gastrointestinal perforations and dyslipidaemia, noted with the 10 mg dose level. It is difficult to justify the additional risks seen in the 10

[35] Sponsor clarification: There was no statistical comparison between the tofacitinib 5 and 10 mg bd doses. The studies were not powered to detect potential differences between doses.

mg group in the absence of any proven improvement in inflammatory markers (ESR) or structural benefit.

The main risk is infection due to the immunosuppressive effect which might be manageable with extensive knowledge and understanding, but the opportunistic infections seen with tofacitinib are rarely seen in the general population. This poses a challenge in diagnosing and managing such infections in a timely and safe manner, and supports the opinion of the clinical evaluator that patients receiving tofacitinib should be under the care of a specialist. The Delegate was satisfied with the response of the sponsor in proposing the text *"Therapy with Xeljanz should be initiated and monitored by a specialist physician with expertise in the management of rheumatoid arthritis"* as part of the indication. The provision of a patient alert card would also assist in alerting both the patients and attending doctors of the increased infection risk.

Given the potential for increased immunosuppressive effect of tofacitinib with other bDMARDs, these should not be used in combination. Additionally, tofacitinib should not be used in combination with other immunosuppressive agents such as azathioprine or cyclosporine.

Caution should be exercised when commencing tofacitinib in patients with known risk factors for gastrointestinal perforation such as diverticulitis, concomitant glucocorticoids or NSAIDs (this is noted in the draft PI).

Given the complexity of the side effect profile, the Delegate was in agreement with the clinical evaluator's suggestion that tofacitinib be used under the guidance of a specialist physician or rheumatologist as management of the risk/benefit of its use requires an extensive understanding of the potential risks and benefits, their identification and management, and knowledge about appropriate treatment alternatives. The RMP identifies the need for appropriate training and evaluation of that training prior to prescribing tofacitinib.

Other risks, such as the impact of the elevated cholesterol levels on CV risk, are uncertain and require longer term data to clarify. Other toxicities, such as abnormal haematological, liver, and renal function tests, may emerge over time with tofacitinib and require monitoring and management. Caution needs to be exercised when prescribing medications that affect CYP3A4 for their potential effect on tofacitinib metabolism and efficacy.

Proposed regulatory action

As a new class of drug (with limited experience of its long term safety) and some improvement in signs and symptoms but no proof as yet in reducing the progression of structural damage (unlike other DMARDs available), and the lower dose (5 mg) having a lesser effect on inflammatory marker levels (ESR), then it may be reasonable to approve tofacitinib in the third line setting, after failure of both a traditional and bDMARD. Patients with progressive RA, for whom all other treatment avenues have been exhausted, may consider the risk/benefit profile acceptable. However, there remain a number of safety concerns with this drug such as gastrointestinal perforations, potential long term CV effects in addition to those predicted for an immunosuppressive agent.

Accordingly, approval for tofacitinib at 5 mg bd could be considered for the following indication:

> *Xeljanz/tofacitinib is indicated for the treatment of moderate-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. In these patients, Xeljanz can be used in combination with methotrexate, or used as monotherapy.*

Data deficiencies

- There needs to be data to demonstrate the relative benefit of tofacitinib compared with other bDMARDs, in both the second and third line settings.
- There needs to be longer term data (minimum 24 months) presented for the mTSS in those on tofacitinib versus placebo to determine whether there is any structural benefit with tofacitinib with either the 5 mg or 10 mg dose levels.
- Longer term data is needed to clarify the CV risk of the dyslipidaemia and hypertension noted in those on tofacitinib.
- Studies including more subjects over 65 years of age need to be conducted to establish risks and benefits in this age group, especially as this is the age group predominantly affected by RA.
- There are no data about tofacitinib in the paediatric population.

The Delegate was not in a position to say, at this time, that the application for tofacitinib should be approved for registration, for the requested indication. However, the following modified indication may be considered for registration:

> *Xeljanz/tofacitinib is indicated for the treatment of moderate-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. In these patients, Xeljanz can be used in combination with methotrexate, or used as monotherapy.*

Request for ACPM advice

The Delegate proposed to request advice from the ACPM and to request the following specific issues in particular be addressed:

- Whether there is considered sufficient additional clinical benefit to offset the risk of increasing side effects, especially serious infections and malignancy, with the proposed option to increase the dose level to 10 mg bd.
- Given the limited efficacy with the twice daily 5 mg dose level, such as no proven benefit in limiting structural damage, whether tofacitinib should be approved as third line only after inadequate response or intolerance to a trial of a traditional and existing bDMARD, which are proven in this regard.
- Whether prescription of tofacitinib should be restricted only to rheumatologists or specialist physicians with an interest in rheumatology.
- Whether a patient alert card should be provided by the sponsor.
- Whether, given the relatively narrow therapeutic window, there is a potential overdose risk of a pack size of 180 (in a PP child proof bottle).

Questions to the sponsor

Additionally, the Delegate requested the sponsor provide the following in their response to the Overview:

1. A table showing which studies, particularly the pivotal efficacy studies, were submitted for evaluation to the committees of each of the following: FDA, EMA, and TGA.
2. A list of the initial and subsequently revised proposed indications in the application made to the EMA.

3. Clarification as to whether the pneumococcal and influenza vaccines used in Study A3921129 and Vaccine Sub-study A3921024 were the same.
4. Clarification: In the long term extension studies, was data on renal function kept for the patients who discontinued tofacitinib or just those who remained on the medication?

Addendum to the delegate's initial overview: Evaluation of clinical data submitted in response to round 3 questions

The following Addendum to the Delegate's initial Overview, dated 2 September 2013, provides the Delegate's evaluation of the sponsor's responses to the Round 3 clinical questions (see above), and contained additional request for advice from the ACPM.

TGA round 3 question 1: Were there any treatment emergent ECG abnormalities in Study A3921069?

In response, the sponsor replied on 27 August 2013 with additional data from Study 1069. Summary tables are presented for the ECG abnormalities at baseline and 12 month visit; the 24 month visit represents patients who completed with an early termination visit as this is a 1 year analysis.

ECG-related adverse events

The number of reported adverse events related to ECG abnormalities for Study A3921069 (1 year report) is listed in Table 28 below (taken from the sponsor's response to Round 3 clinical questions).

Table 28: Abnormal ECG adverse events by treatment through Month 12 (1-Year Analysis)

Event Study Day	MedDRA Preferred Term	Severity	Action Taken	Outcome	Causality
Tofacitinib 5 mg bd					
Study Day 365	Sinus bradycardia	Mild	Weekly ECG Monitoring, Laboratory	Ongoing	Related to study drug
Study Day 363	Sinus bradycardia	Mild	Continued Observation	Resolved Study Day 446	Related to study drug
Study Day 351	Ventricular extrasystoles	Mild	Advised Detailed Cardiac Evaluation	Resolved Study Day 371	Related to study drug
Study Day 351	Electrocardiogram QT prolonged	Mild	Advised Detailed Cardiac Evaluation		

Event Study Day	MedDRA Preferred Term	Severity	Action Taken	Outcome	Causality
Tofacitinib 10 mg bd					
Study Day 364	Sinus bradycardia	Mild	Observation	Ongoing	Related to study drug
Study Day 337	Electrocardiogram ST-T change	Mild	No Action Taken	Ongoing	Not related to study drug
Study Day 360	Electrocardiogram PR prolongation	Mild	Repeat ECG on 02/16/2012	Ongoing	Related to study drug
Study Day 358	Electrocardiogram repolarisation abnormality	Mild	No Action Taken	Resolved Study Day 365	Not related to study drug
Methotrexate 10 to 20 mg/week					
Study Day 281	Atrioventricular block first degree*	Severe	Hospitalisation	Resolved Study Day 293	Not related to study drug
Study Day 36	Worsening Palpitations	Moderate	No Action Taken	Ongoing	Not related to study drug
Study Day 175	Atrial flutter*	Severe	Hospitalisation	Resolved Study Day 184	Not related to study drug

Source: A3921069 Clinical Study Report (1 year report) CSR Tables 14.3.2.2 and 16.2.7 [Modified to redact patient and study date information]. MedDRA (version 15.0) coding dictionary applied. Abbreviations: bd = twice daily, MedDRA=Medical Dictionary for Regulatory Activities, AE=adverse event. *Serious adverse event, according to investigator assessment.

In summary, there were 4 AEs in 3 subjects in the tofacitinib 5 mg dose group at 12 months, all deemed related to the study drug. One of these events was clinically significant with QT prolongation of 89 msec (QTc 521 msec, compared with 432 msec at baseline) associated with ventricular extrasystoles on Day 351 of the study drug. The tofacitinib was discontinued with resolution of the QT prolongation. The study drug was recommenced on Day 371 with an observed increase in QTc interval above the baseline and Day 371 recordings (see Table 29 below). Tofacitinib 5 mg bd was continued until completion on Day 771 but no additional clinical AEs have been reported in this patient by the sponsor.

Table 29: The ECG values of the patient on tofacitinib 5 mg bd: ECG values during A3921069 Study

ECG					
		24JAN2011	07FEB2012	27FEB2012	09FEB2013
		(-28)	(351)	(371)	(719)
Test	Unit	Result	Result	Result	Result
HEART RATE	bpm	68	90	71	61
PR INTERVAL	msec	142	128	142	150
QRS COMPLEX	msec	82	80	84	86
QT INTERVAL	msec	402	422	398	452
QTC INTERVAL	msec	432	521	437	461
QTCB INTERVAL (BAZETT'S CORRECTION	msec	428	517	433	456
RR INTERVAL	msec	882	668	841	978

In the 10 mg tofacitinib group, there were 4 AEs with 2 related to study drug, and 3 events in the MTX group, none thought to be study drug-related.

Additional data was supplied about the baseline ECG characteristics of those entering Study A3291069 by treatment group. The baseline QTcF was similar across the tofacitinib 5 mg dose level (5% with QTcF > 450 msec), 10 mg dose level (5.3 % with QTcF >450 msec) and MTX (5.1% with QTcF > 450 msec).

At the 12 month report of ECG abnormalities, the percentages of subjects with an increase in QTcF > 60 msec were 2.7% of subjects on 5 mg bd and 3.9% in the 10 mg dose level compared with 0.8% taking MTX. There was no placebo group in this study.

The table reporting the 24 month review only incorporates those with an early termination visit, thus does not reflect the entire study population enrolled. Compared with the data set for visit 7 (12 month), ECG data were only available for 15% of those receiving tofacitinib 5 mg bd, 15% of those on the 10 mg dose level and 31% of the MTX group. Of these subjects with abnormal ECGs, an increase of > 60 msec in QTcF was observed in 11.4% in the 5 mg group (including 3 patients with QTcF > 500 msec), 6.8% in the 10 mg group and 7.5% in the MTX group. No subjects in the 10 mg dose level or MTX group had QTcB > 500 msec. However, this dataset is incomplete and requires the data from the remaining subjects in each arm of this trial to evaluate the number of episodes of serious ECG abnormalities including QT interval prolongation.

TGA round 3 questions 2-4:

For the remainder of the questions, the sponsor replied as follows:

Question 2: The data for the Vaccine Study (A3921024) had not been offered for evaluation in Rounds 1 and 2 of the TGA evaluation process, as it was submitted in response to a clinical question raised after the [evaluation phase cut-off date]

Question 3: Study A3921152 has completed last subject, last visit, but neither the final tables nor the clinical study report (CSR) are currently available or completed.

Question 4: The patient with potential DILI referred to in its response to the CHMP is the same case referred to in the response to the TGA Round 1 questions.

Safety discussion

The above ECG data sets are only complete for the baseline and 12-month visit, and indicate that there is an increase in the QTc of at least 60 msec from baseline in both tofacitinib arms (5 mg or 10 mg) after commencing this drug. Furthermore, 1% of subjects in each of the tofacitinib arms had a QTc > 500 msec at the 12 month analysis (although it is not clear whether this was pre-existing or developed while on the drug (see question for sponsor below) while none was seen in the MTX arm. There was one reported serious

adverse cardiac event which was related to the drug induced QT prolongation observed. Although the thorough QT/QTc studies done prior to Phase III did not suggest an increased risk, these latest safety data are a signal of concern as defined by the ICH guideline CHMP/ICH/2/04 ICH *Topic E 14 Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*, which has been adopted for use in Australia.

There does not appear to be a significant clinical risk of QTc interval prolongation with Humira.

The clinical evaluator has seen the data and responded to the TGA on 2 Sept 2013: *"Although this is not a clear indication that tofacitinib is associated with prolongation of the QT interval, the risk benefit assessment was already marginal. This additional concern changes my assessment of the risk benefit and in my opinion more data are required before I could recommend approval for tofacitinib."*

Proposed regulatory action: updated

As a consequence of this additional information and with the need for further data, the Delegate was not in a position to say, at this time, that the application for tofacitinib should be approved for registration, for the requested indication or the amended indication described in the initial Overview (see above).

Request for ACPM advice: updated

The Delegate proposed to request the ACPM provide advice on the following specific issue, in addition to the matters set out in the Delegate's initial Overview of 29th August:

- Whether the proportion of patients experiencing QT prolongation on tofacitinib observed in the safety data supplied 27th August 2013 pose sufficient clinical risk to offset any potential clinical benefits of tofacitinib 5 mg bd.

Additional questions to the sponsor

Following review of the sponsor's responses to Round 3 Question 1 (above), the Delegate requested the sponsor address the following additional questions in relation to the findings from Study A3921069, in addition to those set out in the Delegate's initial Overview of 29th August:

1. What concurrent medications was the subject taking at the time of the adverse event (Day 351), and at the time of recommencement (Day 371) and thereafter? Is there any known CYP3A4 interaction between any medications being taken concurrently at these times? Did the patient have any other abnormalities at the time of the adverse event eg abnormal liver functions tests, renal impairment? Did the patient have a history of any additional factors for QT prolongation? What were the QT intervals during other ECG recordings taken between recommencement (Day 371) and completion (Day 771). Is the patient still taking tofacitinib?
2. Did the subjects with QTc > 500 msec actually receive tofacitinib doses?
3. Are the patients with QTc > 500 msec at the 12 month analysis the same subjects who had the baseline recording > 500 msec at baseline?
4. How many patients developed a QTc > 500 msec while on either dose of tofacitinib?
5. What other timepoints were the ECGs taken and what were the results?
6. Did the patients who developed an increase in QTc prolongation > 60 msec or those who had an absolute QTc interval > 500 msec have any other additional risk factors

for QT prolongation? Were they taking concomitant medications, or have hepatic or renal impairment, that might affect the metabolism or clearance of tofacitinib?

7. When will the complete 24 month ECG data for Study A3921069 become available?
8. What were the reasons for these patients terminating the study early?
9. The sponsor is requested to explain why this ECG safety study data was presented at this late stage, and the reasons underlying this study being undertaken.
10. The sponsor is requested to provide equivalent ECG data from the other pivotal efficacy studies.
11. The sponsor is requested to provide a post-hoc analysis of equivalent ECG safety data across the entire safety database, plus any additional longer term data for ECG safety.
12. How many sudden deaths have there been in patients on tofacitinib?

It was agreed that the evaluation process would be suspended (via a mutually agreed 'stop-clock') to allow the sponsor time to respond to questions and issues raised in the Delegate's initial Overview and Addendum.

Sponsor's response to the delegate's initial overview

The following is part of the sponsor's response to questions and issues raised in the Delegate's initial Overview and Addendum (above). The data provided in response to specific questions and issues are evaluated by the clinical evaluator in the Fourth round evaluation report (see AusPAR Attachment 4); the evaluator's assessment of the sponsor's responses to specific questions raised in the Delegate's Overview and Addendum are below under *Fourth round evaluation of clinical data submitted in response to questions*.

Background information

The sponsor acknowledges and agrees with the positive recommendation given by the clinical evaluator for the use of tofacitinib in a second line setting, following the First and Second round assessments of the application to register the product. As stated by the clinical evaluator *"The benefit-risk balance of tofacitinib, given the proposed usage, is favourable"*.

Subsequent to a negative CHMP opinion received in Europe (April 2013) for the application to register tofacitinib, a mutual 'stop-clock' was agreed between the sponsor and the TGA, to allow additional information to be provided by the sponsor. As a result, a Third round clinical evaluation was undertaken by the TGA and the CER was issued to the sponsor. In this Third round CER, the clinical evaluator noted additional efficacy outcomes for tofacitinib and an absence of new safety concerns, but recommended approval of tofacitinib in a third line setting, aligning with the indication which the sponsor had proposed in Europe only, solely in response to concerns expressed by the CHMP.

The Delegate supported the clinical evaluator's recommendation and had initially sought ACPM advice for approval in a third line setting. However, following an additional concern raised by the clinical evaluator regarding potential QT interval prolongation with tofacitinib, the Delegate issued an addendum to the Delegate's Overview in which neither a second nor third line indication were considered favourable.

Concerns raised by TGA delegate

The Delegate has raised a number of concerns regarding the data supporting the application, which the sponsor seeks to fully address. The sponsor firmly believes that adequate data are available to address the Delegate's concerns and that the data presented

in this response document provides additional evidence to confirm a positive benefit-risk for tofacitinib.

The Delegate sought the following advice from the ACPM:

- Whether there is considered sufficient additional clinical benefit to offset the risk of increasing side effects, especially serious infections and malignancy, with the proposed option to increase the dose level to 10 mg bd.
- Given the limited efficacy with the twice daily 5 mg dose level, such as no proven benefit in limiting structural damage, whether tofacitinib should be approved as third line only after inadequate response or intolerance to a trial of a traditional and existing bDMARD, which are proven in this regard.
- Whether prescription of tofacitinib should be restricted only to rheumatologists or specialist physicians with an interest in rheumatology.
- Whether a patient alert card should be provided by the sponsor.
- Whether, given the relatively narrow therapeutic window, there is a potential overdose risk of a pack size of 180 (in a polypropylene (PP) child proof bottle).

The Delegate sought the following advice in the Addendum to the Overview:

- Whether the proportion of patients experiencing QT prolongation on tofacitinib observed in the safety data supplied 27th August 2013 pose sufficient clinical risk to offset any potential clinical benefits of tofacitinib 5 mg bd.

Line of therapy sought in Australia

The Australian application continues to seek registration of tofacitinib as a second line therapy for moderate to severe active RA, that is, in adults who have had an inadequate response or are intolerant to previous DMARD therapy. The sponsor proposes the following indication:

> *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. Xeljanz can be used alone or in combination with non-biological DMARDS, including methotrexate. Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis."*

The application dossiers submitted to the EMA, the TGA, and all other regulatory agencies, including the US FDA, contained a core group of 5 Phase III pivotal studies collectively representing the primary source of safety and efficacy data to support health authority review of tofacitinib for the treatment of RA. Four of the 5 pivotal studies included in the dossier were conducted in 2705 patients with moderate to severe RA who were DMARD inadequate responders, the large majority of whom were MTX inadequate responders (MTX-IR). DMARD inadequate responders are considered a "second line" population, as they have had an inadequate response to traditional first line therapies. There is significant unmet medical need amongst RA patients who are considered DMARD inadequate responders, and the tofacitinib studies in this population collectively provide the clinical evidence supporting the second line indication proposed by Pfizer. The remaining Phase III pivotal study in the dossier was conducted in TNF inhibitor inadequate responders, which is considered to be a "third line" population.

While Pfizer continues to believe that the preponderance of evidence supports use of tofacitinib as a second line therapy, the indication was modified specifically for the marketing authorisation application (MAA) in Europe based on feedback received during the review process and in an attempt to find a conservative, compromise position that

would make tofacitinib initially available only to "third line" European RA patients with higher unmet medical need than "second line" patients.

On the basis of the evidence, tofacitinib has been approved as a second line therapy in a number of countries worldwide with major approvals in the United States, Switzerland and Japan.

Benefit-risk

Pfizer maintains that the overall benefit–risk of tofacitinib is appropriate for use in second line RA patients, consistent with marketing authorisation applications that have been submitted, and consistent with marketing authorisation approvals for tofacitinib that have been granted to date. Pfizer believes that the available evidence, now including over 12,000 patient-years of experience, predominantly in the second line population, supports approval of the 5 mg bd dose in Australia for RA patients who have had an inadequate response to DMARD therapy.

The Delegate notes in the Overview that: *"a significant increase in toxicity with increasing dose with more adverse events, especially infections, risk of malignancy, gastrointestinal perforations and dyslipidaemia, noted with the 10 mg dose level" and "Although there appeared to be a trend towards an increased efficacy in some studies with the 10 mg dose, in the five phase III placebo-controlled studies, there was no significant difference in efficacy was [sic] demonstrated between the 5 mg and 10 mg dose levels."*

To remove from consideration any uncertainty about the benefit-risk profile for the 10 mg bd dose, the sponsor does not wish to pursue the registration of tofacitinib 10 mg bd, until further data are available.

As seen with other approved therapies that reduce the inflammation underlying RA, tofacitinib has safety findings and potential risks that reflect its immunomodulatory mechanism of action. The sponsor believes that the rate and type of adverse events seen with tofacitinib in the RA program are consistent with those seen with biologic DMARDs approved in Australia as first and second line therapies.

Australian rheumatologists, with their extensive experience in the use of biologic agents and understanding of the benefits and risks of immunomodulatory therapies, are well familiar with these types of adverse events and best placed to effectively manage tofacitinib appropriately. Thus, the sponsor agrees with the Delegate's view that tofacitinib should be used under the guidance of a specialist physician or rheumatologist.

To assist the appropriate management of the risks, the sponsor has proposed a risk mitigation plan to further communicate the risks to both healthcare professionals (HCPs) and patients, including an educational program and a patient medication alert card.

Safety

QT prolongation

In the Delegate's Addendum to the Overview, the following advice was sought from the ACPM: *"Whether the proportion of patients experiencing QT prolongation on tofacitinib observed in the safety data supplied 27th August 2013 pose sufficient clinical risk to offset any potential clinical benefits of tofacitinib 5 mg bd".*

Convincing evidence exists that tofacitinib treatment is not associated with an increase in potential torsadogenic (that is, pro-arrhythmic) risk. A detailed discussion of ECG/QTc findings across the entire tofacitinib program is provided for evaluation[36].

[36] See Fourth Round clinical evaluation report (AusPAR Attachment 4) for evaluation of these data

The sponsor understands that some of these safety data at face value may give rise for concern but is confident that the following detailed explanation will alleviate any concerns regarding clinical risk.

The Delegate states in the Addendum to the Delegate's Overview that *"Although the thorough QT/QTc studies done prior to Phase III did not suggest an increased risk, these latest safety data are a signal of concern as defined by CHMP/ICH/2/04 ICH Topic E 14 Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, which has been adopted for use in Australia". The Delegate also comments that the data "indicate that there is an increase in the QTc of at least 60 msec from baseline in both tofacitinib arms (5 mg or 10 mg) after commencing this drug."*

The latest safety data to which the Delegate refers were provided in response to the question raised in the Third Round evaluation report *"Were there any treatment emergent ECG abnormalities in Study A3921069?"*.

The following section outlines the QTc changes in Study A3921069:

- Increases in QTc of 30 to 60 msec and ≥ 60 msec from baseline were observed in both tofacitinib arms and the MTX arm
  - At Month 12, the percentage of patients with an increase from baseline in QTcF of 30 to 60 msec was numerically higher for MTX (12%) compared to tofacitinib 5 mg (10.9%) and 10 mg (10.9%)
  - At Month 12, the percentage of patients with an increase from baseline of ≥ 60 msec was numerically higher for tofacitinib 5 mg (2.7%) and 10 mg (3.9%) than MTX (0.8%)
  - At Month 24, the percentage of patients with increases of either 30 to 60 msec or ≥ 60 msec in QTcB and QTcF were similar in all treatment groups
- The mean change from baseline was similar across treatment groups for QTcB and QTcF
- The MTX-subtracted change from baseline for either QTcF or QTcB indicated no difference between tofacitinib and MTX-treated patients
- No clinically relevant changes occurred and no trends were apparent across study groups in QTcF and QTcB intervals.

The observed ECG outliers in Study A3921069 are clearly isolated instances when considering the totality of the QT evidence across the RA program and in light of the in vitro electrophysiological data. Interpreting outliers of ECG changes in patients depends upon the body of evidence linking the drug with (1) effects on repolarising potassium currents (for example, human ether-a-go-go related gene (hERG)) in vitro, and (2) QTc changes measured in normal volunteers under carefully controlled conditions wherein concomitant medications and underlying disease are absent, and where a positive control for assay sensitivity (that is, Thorough QT study) can be implemented.

Tofacitinib has little or no effects on either category of evidence. Both academic electrophysiology experts and regulatory experts agree that in the absence of findings on the normal ECG or repolarising currents, outlier ECG changes seldom if ever predict pro-arrhythmic risk of a drug. Instead, the many confounding factors that alter the ECG intervals, such as autonomic tone, underlying slurring or flattening of the ST-T waves, body position, concomitant medications, are the most likely aetiologies of outlier values. This becomes increasingly likely as data from all studies are integrated and no imbalances are revealed.

Data from Study A3921069 as discussed above as well as data from across the entire tofacitinib development program strongly support that tofacitinib is not associated with an increase in potential torsadogenic (that is, pro-arrhythmic) risk, as outlined below:

- In nonclinical studies at concentrations in excess of therapeutic concentrations, tofacitinib had no effect on hERG current or cardiac repolarisation in dog Purkinje fibres in vitro or in cynomolgus monkeys in vivo
- The results of the Thorough QT/QTc study' (TQT) conducted with tofacitinib in accordance with ICH E14 *The Clinical Evaluation of QT/QTc Interval Prolongation and Pro-arrhythmic Potential For Non-Antiarrhythmic Drugs* (Study A3921028) were negative
  - In the TQT study of a single dose of 100 mg tofacitinib (with approximately 5 times higher maximum plasma concentration at steady state (Cmax) compared to that of 10 mg bd in RA patients), both the means and the upper limits of the 2-sided 90% CI were below 5 msec at all post-dose time points confirming that there is an absence of an effect on the QTc interval by tofacitinib.
  - Regarding interpretation of the TQT, section 2.2.4 of ICH E14 states *"...drugs that prolong the mean QT/QTc interval by around 5 msec or less do not appear to cause TdP."* TGA has adopted the ICH E14 Guideline with the following annotation *"QT prolongation would be of regulatory concern if either the estimated QT prolongation was > 5 msec OR the upper bound of the 95% confidence interval was > 10 msec."*
  - Negative results of a "thorough QT/QTc study" are a very good predictor of low potential for drug-induced torsades de pointes (TdP).
- The absolute mean change from baseline and the incidence of outliers for QTc and QRS intervals were similar among tofacitinib dose arms and placebo for the Phase II studies and the Phase III study where ECG interval measurements were collected. The absolute value of these parameters and the number of outliers with respect to change from baseline did not increase over time for any treatment group.
  - In the tofacitinib RA Phase I, Phase II and completed Phase III studies in which ECG information was collected there was no evidence of clinically relevant prolongation of the QT interval
  - The absolute mean change from baseline and the incidence of outliers for QTc intervals were balanced across treatment groups that included placebo, MTX, and/or adalimumab.
- There was no association between tofacitinib and clinically significant changes in ECG waveform or QT/QTc interval prolongation over a large multiple of tofacitinib drug concentrations (approximately 5 times the steady state peak plasma concentration of a 10 mg bd dose in RA patients)
- Adverse events coding to the standardised MedDRA query (SMQ) of TdP/QT prolongation in the RA tofacitinib clinical development program were infrequent and balanced across treatment groups, with no occurrences of torsades de pointes.

In summary, there is no evidence of clinically relevant prolongation of the QT interval in the Phase I, II and III studies of the overall tofacitinib RA program. Furthermore the TQT study in healthy volunteers in which the estimated adjusted mean difference was below 5 msec at all post dose time points has further confirmed that there is an absence of an effect on the QTc interval by tofacitinib. Finally, in nonclinical studies at concentrations in excess of therapeutic concentrations, tofacitinib had no effect on hERG current or cardiac repolarisation in vitro or in vivo.

Given the weight of the evidence overall, the proportion of patients experiencing QT prolongation on tofacitinib observed in the A3921069 safety data supplied 27th August 2013, is highly unlikely to represent a clinical risk that would offset any potential clinical benefits of tofacitinib 5 mg bd.

Safety events of interest

The types and frequency of AEs seen in the RA program are comparable to those seen with therapies currently approved in Australia and are familiar to physicians who treat patients with RA. Table 30 shows incidence rates for selected safety events of interest with tofacitinib 5 mg bd in the Phase III and long term extension studies as of April 2013.

Table 30: Cumulative incidence rates (events/100 patient-years) for selected safety events of interest in Phase III controlled and long term extension studies: Tofacitinib 5 mg bd and placebo

Parameter	Phase 3 Controlled Studies†		Long Term Extension Studies Tofacitinib 5 mg BD			
	Tofacitinib 5 mg BD	Placebo	*29 Mar 2011§*	*29 Sep 2011§*	*19 Apr 2012§*	*10 Apr 2013§*
Total Patients	1216	681	1321	1370	1421	1452
Total Patient Years	904	203	2236	2726	3243	4005
	Incidence Rate(95% CI)					
Adverse Events Resulting in Discontinuation	10.58 (8.65, 12.94)	12.41 (8.38, 18.36)	6.66 (5.67, 7.82)	6.39 (5.50, 7.41)	6.55 (5.72, 7.49)	NA
SAE	11.87 (9.79, 14.38)	15.02 (10.51, 21.49)	10.28 (9.00, 11.74)	9.65 (8.52, 10.93)	9.80 (8.75, 10.99)	9.52 (8.57, 10.57)
Mortality (up to 30 days of last dose)	0.55 (0.23, 1.33)	0.49 (0.07, 3.51)	0.36 (0.18, 0.72)	0.37 (0.20, 0.68)	0.31 (0.17, 0.57)	0.33 (0.19, 0.56)
Serious Infections	3.22 (2.24, 4.63)	1.48 (0.48, 4.59)	2.25 (1.71, 2.97)	2.33 (1.82, 2.99)	2.62 (2.11, 3.24)	2.5 (2.05, 3.05)
Tuberculosis	0	0	0.045 (0.006, 0.32)	0.073 (0.018, 0.29)	0.154 (0.064, 0.37)	0.15 (0.07, 0.33)
Opportunistic Infections*	0.33 (0.11, 1.03)	0	0.36 (0.18, 0.72)	0.37 (0.20, 0.68)	0.40 (0.23, 0.69)	0.38 (0.23, 0.62)
Herpes Zoster	4.39 (3.21, 6.01)	1.49 (0.48, 4.61)	4.25 (3.46, 5.22)	4.09 (3.38, 4.95)	4.18 (3.51, 4.97)	4.0 (3.41, 4.7)
Malignancies (excluding NMSC)	0.55 (0.23, 1.33)	0	1.03 (0.68, 1.55)	1.07 (0.74, 1.53)	1.02 (0.72, 1.43)	1.02 (0.75, 1.39)
Nonmelanoma Skin Cancer	0.33 (0.11, 1.03)	0.99 (0.25, 3.95)	0.36 (0.18, 0.72)	0.37 (0.20, 0.68	0.31 (0.17, 0.58)	0.35 (0.21, 0.59)
LPD/ Lymphoma	0	0	0.089 (0.022, 0.36)	0.073 (0.018, 0.29)	0.062 (0.015, 0.25)	0.075 (0.024, 0.23)
GI Perforation	0	0	0.18 (0.07, 0.48)	0.15 (0.06, 0.39)	0.12 (0.05, 0.33)	NA
Composite MACE	0.44 (0.17, 1.18)	0.99 (0.25, 3.95)	0.17 (0.056, 0.53)	0.18 (0.067, 0.48)	0.29 (0.15, 0.58)	0.34 (0.19, 0.60)

Apr=April; BD=twice daily; CI=confidence interval, AE=adverse event, DC=discontinuation; GI = gastrointestinal; LPD=lymphoproliferative disease; Mar=March; N=number of patients; NMSC=nonmelanoma skin cancer, MACE= major adverse cardiovascular event, NA=not available; pt-yr=patient years; SAE=serious adverse events; Sep=September
† Includes protocols A3921032, A3921044(1 year analysis), A3921045, A3921046 and A3921064; § Date of data cut off; * Comprises opportunistic infections plus tuberculosis

Overall rates of AEs, DAEs, SAEs and mortality were comparable between tofacitinib at the 5 mg bd dose level and placebo, with no increase in event rates over time with increased exposure to tofacitinib. Specific safety considerations noted in the Delegate's Overview are discussed in more detail in the following sections.

Serious infections

The Delegate states *"In the pivotal studies which utilised the dose being sought in this application, one in three of the trials where tofacitinib was added to MTX (1064) yielded an increased rate of serious infections in the tofacitinib groups compared with placebo or adalimumab; in the other two trials, the rates did not vary between treatment arms (1032, 1044)".*

In Study A3921064, there were 3/204 (1.47%) patients with a serious infection in the adalimumab treatment group and 7/204 (3.4%) patients on tofacitinib 5 mg, yielding an odds ratio of 2.4 (95% CI 0.53, 14.4). However, no conclusion on the relative risk of serious infections between tofacitinib and adalimumab can be drawn on the basis of this study alone, given the limited number of patients in the adalimumab group compared to the number of patients who received tofacitinib across the overall clinical program, and the paucity of cases in either treatment group and limited exposure period in this study. The CI of the odds ratio is wide and includes unity, precluding any within study conclusion on comparative rates.

To better contextualise the rate of serious infections seen with tofacitinib, a meta-analysis was performed to compare incidence rates from studies of approved biologic DMARDs to those observed in the tofacitinib clinical development program[37].

This meta-analysis revealed that the observed rate of serious infections for adalimumab in Study A3921064 appears low compared to other published clinical trial data for adalimumab and other approved biologic therapies. Given the robust patient-years of exposure in this comprehensive analysis, the sponsor believes that patients receiving tofacitinib at the 5 mg bd dose have similar rates of serious infections to biologic DMARDs.

Herpes zoster

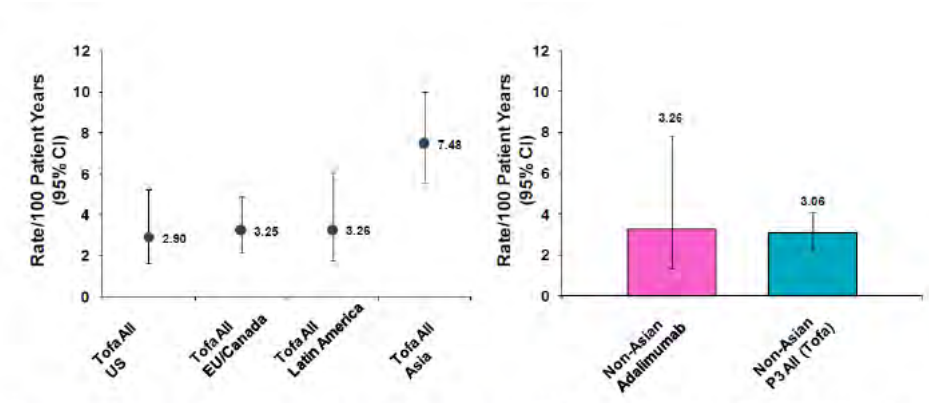
The updated overall incidence rate for herpes zoster in Phase III studies (10 April 2013 data cut) was 3.85 events/100 patient-years (95% CI 2.96, 5.02) in tofacitinib 5 mg treated patients, which was 1.4 fold higher than the Phase III Study A3921064 adalimumab rate (2.8 [95% CI 1.17, 6.76]) and higher than rates typically reported for other RA therapies (Strangfeld et al. 2009[38]).

However, the majority of herpes zoster events in patients receiving tofacitinib were reported as non-serious cases. The proportion of patients with serious or multidermatomal/ophthalmic herpes zoster was small (6/55 were serious or multidermatomal/ophthalmic), and consistent with published rates for biologic DMARDs (Strangfeld et al. 2009).

Overall, the majority of patients (89.7% [35/39] in Phase III studies at 5 mg) with herpes zoster events did not require permanent discontinuation from study drug and all responded to conservative management with appropriate medical treatment if needed.

Although population data is limited, it should be noted that an evaluation of geographic region and race revealed a lower rate of herpes zoster in tofacitinib patients treated in non-Asian regions compared to those treated in Asia. There were similar rates of herpes zoster between non-Asian patients treated with tofacitinib and non-Asian patients treated with adalimumab in Phase III Study A3921064 (see Figure 2 below, from the *FDA Advisory Committee Meeting Tofacitinib for the Treatment of Rheumatoid Arthritis (NDA 203214) Briefing Document* 9 May 2012). None of the 19 Asian patients living in non-Asian countries reported herpes zoster.

Figure 2: Rate of herpes zoster by geographic region and in non-Asian race treatment groups



Non-Asian Adalimumab=Non-Asian patients in the adalimumab group; Non-Asian P3All (Tofa)l=Non-Asian tofacitinib patients in the Phase 3 studies; Tofa All US= all tofacitinib patients from study sites in the United States; Tofa All EU/Canada= all tofacitinib patients from study sites in the European Union and Canada; Tofa All Latin America= all tofacitinib patients from study sites in Latin America; Tofa All Asia: all tofacitinib patients from study sites in Asia

[37] See Fourth Round clinical evaluation report (AusPAR Attachment 4) for evaluation of these data
[38] Strangfeld A. et al. Risk of Herpes Zoster in Patients With Rheumatoid Arthritis Treated With Anti–TNF-alfa Agents. *JAMA* 2009;301(7):737-744

Malignancies

Malignancies were infrequent in Phase III and long term extension studies and were consistent across active treatment groups. There was no increase in the incidence of malignancies with increased cumulative exposure. In the 5 Phase III studies pooled data, the malignancy rates were similar between tofacitinib 5 mg bd and adalimumab. The Standardised Incidence Ratio (SIR) for all malignancies (excluding non-melanoma skin cancer (NMSC)) as compared with the US Surveillance Epidemiology and End Result (SEER) database is 1.08 (95% CI 0.89, 1.31) indicating no increase compared with the general US population.

To contextualise the rate of malignancy seen with tofacitinib, a meta-analysis was performed to compare incidence rates from studies of approved biologic DMARDs to those observed in the tofacitinib clinical development program.

This comprehensive meta-analysis revealed similar malignancy rates for tofacitinib 5 mg and 10 mg bd compared to other currently available biologic DMARDs. Sensitivity analyses concluded that the inclusion/exclusion criteria of the studies did not impact the estimates.

Lymphoma

The Delegate states *"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"*. The sponsor notes that certain cancers have been reported to occur at higher frequency in patients with RA compared to the general population, regardless of treatment modality, including Hodgkin's and non-Hodgkin's lymphoma, leukaemia and myeloma. The risk of malignancies, including lymphoma, is a concern with all therapeutic agents that treat RA by modulation of the immune system, including approved biologic DMARDs; however, it is not clear whether the risk of lymphoma is increased further by methotrexate or TNF inhibitor agents. Some studies have concluded that the use of DMARDs was not associated with lymphoma risk (Baecklund, 2004; Baecklund, 2006). Baecklund, et al, concluded that a high level RA disease activity coupled with a long duration of disease is associated with a greater risk of lymphoma. Thus, any inference that a higher risk of lymphoma compared to the background (non-RA) population is indicative of a causative risk with tofacitinib is premature.

In tofacitinib RA trials, the SIR for lymphoma, while elevated compared to the general (non-RA) population, is consistent with those reported in RA trials of biologic DMARDs currently approved in Australia and likely represents the role of the underlying disease on lymphoma risk.

Long term extension studies revealed no increase in the incidence of lymphoma with increased cumulative exposure to tofacitinib (Table 30).

Gastrointestinal perforations

Medications used to treat RA, including NSAIDs, glucocorticoids, and DMARDs, have all been associated with increased risk of GI perforation. All patients with GI perforations in the tofacitinib RA program had associated risk factors including concomitant use of NSAIDs and/or glucocorticoids. Several of the events occurred in the setting of diverticulitis, also a known risk factor.

In the Phase III program there were no GI perforations at the 5 mg bd dose level; in the long term extension studies there were 4 cases at the 5 mg bd dose level with an incidence rate 0.12 per 100 patients-years. The incidence rates for GI perforations seen with tofacitinib are comparable to those reported for biologic DMARDs. In particular, they appear lower than the rate seen with tocilizumab (0.28 events per 100 patient-years, Actemra Australian PI), a biologic DMARD approved in Australia as a first line therapy. Further to this, the sponsor notes the Delegates comment that *"The EMA identified that this risk profile was consistent with other biologic agents such as etanercept and tocilizumab"*.

Liver function

The Delegate states *"There was one death due to hepatic failure in a patient who had received 10 mg bd tofacitinib; despite discontinuation of the tofacitinib, the LFTs worsened after 2-3 months with the pattern of liver injury potentially drug-related. The sponsor reports that it was difficult to determine whether this was a drug-induced liver injury or autoimmune hepatitis as there was some improvement with corticosteroids and azathioprine".*

The sponsor wishes to clarify the clinical outcome for this patient described in the Delegate's Overview. The patient did not die. Indeed, at last report, the patient was doing well with a tapering dose of corticosteroids and azathioprine. The investigator has indicated that the azathioprine dose would be maintained for two years on the advice of the hepatologist to prevent recurrence of autoimmune hepatitis. The ALT, AST, total bilirubin, and international normalised ratio (INR) (laboratory evaluations collected June 2012) were within the normal reference ranges.

The sponsor notes that while increases in hepatic transaminases were observed in patients treated with tofacitinib, they occurred with similar frequencies in all treatment groups and increases > 3 x ULN were uncommon. As expected, elevations were more common in patients treated with concomitant DMARDs (most commonly MTX).

The incidences of transaminase values as multiples of the ULN were lower in patients treated with tofacitinib 5 mg bd than in patients treated with MTX in Study A3921069, suggesting that the transaminase elevations observed with tofacitinib in the Phase III studies in the initial submission were associated with background MTX treatment.

As previously noted, the frequency of transaminase elevations with tofacitinib is consistent with those reported in RA patients treated with approved biologic therapies (Ghabril 2013). Frequencies of liver enzyme elevations were compared between tofacitinib and tocilizumab treatments; the frequencies of liver enzyme elevations appear lower in patients treated with tofacitinib than those treated with tocilizumab, an agent approved as a first line therapy in Australia.

Lipid changes and cardiovascular events

The sponsor notes the Delegate's comment that *"The evidence for dose-related dyslipidaemia is more compelling, with reports of increased LDL-C and triglycerides"*.

Dose dependent increases in total cholesterol, LDL-C and HDL-C were observed in RA patients receiving tofacitinib. These occurred within 1-3 months of initiation of treatment with tofacitinib and remained stable thereafter with continued tofacitinib treatment.

The sponsor notes that similar increases have been reported with other approved first or second line therapies. According to the Australian PI for tocilizumab, *"Approximately 24% of patients receiving Acterma in clinical trials experienced sustained elevations in total cholesterol > 6.2 mmol/L (240 mg/dL), with 15% experiencing a sustained increase in LDL to ≥ 4.1 mmol/L (160 mg/dL)"*.

In addition, there is no evidence from the clinical development program that tofacitinib is associated with an increase in CV events. Incidence rates for all cause and CV mortality and CV events in ongoing tofacitinib studies are within the rates expected for an RA population and comparable to those observed with the placebo and adalimumab groups in the development program

Lymphocyte counts

The Delegate comments *"The sponsor reports 0.31% patients in this long term safety group receiving 5 or 10 mg of tofacitinib had confirmed absolute lymphocyte counts > 0.5 x 10^9 cells/L". The sponsor wishes to correct an error in this sentence, which should read "…absolute lymphocyte counts < 0.5 x 10^9 cells/L".*

In relation to the incidence of lymphopaenia seen with tofacitinib treatment in the long term extension studies, the sponsor has proposed recommendations in the PI for monitoring of lymphocyte levels at baseline and 3 monthly during treatment, and the recommendation to discontinue therapy in any patient who develops a lymphocyte count < 0.5 x 10^9 cells/L, to mitigate any associated risk of serious infection.

Safety conclusion

In summary, the safety profile of tofacitinib is comparable to other biologic DMARDs approved as first or second line agents in Australia, and is familiar to rheumatologists and specialist physicians with expertise in the management of RA. The types and frequency of AEs seen in the tofacitinib development program are comparable to those seen with these immunomodulating therapies and remain stable over time.

The safety profile of tofacitinib 5 mg bd is well defined for a drug at pre-authorisation stage and can be managed according to the proposed PI and RMP. The sponsor is committed to carrying out additional pharmacovigilance and risk minimisation measures to address any remaining uncertainties.

Efficacy

Clinical and structural efficacy has been demonstrated for tofacitinib as a second line therapy

Tofacitinib has been studied extensively across multiple lines of therapy. The patient-years of exposure to tofacitinib substantially exceed that specified in the TGA adopted guidance CHMP/EWP/556/95 rev 1 *Points to Consider on Clinical Investigation of Medicinal Products Other than NSAIDs for Treatment of Rheumatoid Arthritis.* The EMA Guidelines state *"Usually 300 to 600 patients (with current methodology as a minimum) should be exposed to the proposed marketing dose for 6 months and at least 100 patients exposed at this dose or above for a minimum of 12 months".*

Clinical data has now been presented to the TGA from 4,260 patients in Phase II and III studies requiring inadequate response to DMARD therapy at baseline (second line therapy), 958 patients in a MTX-naïve Phase III study (first line therapy) and 399 patients in a Phase III study requiring inadequate response to a TNF inhibitor biologic agent at baseline (third line therapy). The most recent data cut of 19 April 2012 provided to the TGA represented 4789 patients and 8460 patient-years of exposure. Thus, the available data for tofacitinib is substantially greater than that required by the EMA Guidelines, with the bulk of the evidence being in the second line setting for which registration is sought.

The sponsor agrees with the Delegate's assessment that the efficacy of tofacitinib 5 mg and 10 mg bd has been established both as monotherapy and in combination with MTX or other DMARDs, in reducing clinical signs and symptoms in patients with moderate to severe RA. The sponsor also concurs with the Delegate's view that *"It has been shown to be similar in effect to the TNF-alpha inhibitor, adalimumab"*, a bDMARD registered for use as a first line therapy in Australia. This is supported by a recently published independent meta-analysis that concluded that tofacitinib appears to have comparable efficacy to adalimumab (Kawalec et al., 2013).

However, the sponsor strongly disagrees with the Delegate's opinion that efficacy in halting radiographic progression and reducing inflammatory marker levels is unproven.

Effect on structural progression

The Delegate has stated that *"...it has not been adequately established that tofacitinib has any significant effect on limiting structural joint damage"*.... *"....the 5 mg dose did not have a significant effect on limiting structural damage at 6 months in one study (1044)" and "There needs to be longer term data (minimum 24 months) presented for the mTSS in those on*

tofacitinib versus placebo to determine whether there is any structural benefit with tofacitinib with either the 5 mg or 10 mg dose levels."

Evidence of tofacitinib's inhibition of structural damage progression has been demonstrated both in patients who have had an inadequate response to MTX (Study A3921044) and who are MTX naïve (Study A3921069). Both tofacitinib studies demonstrated less progression in mTSS (primary radiographic endpoint) and JSN (a component of the mTSS and a secondary radiographic endpoint), at both 5 and 10 mg doses up to 24 months, compared to the respective control arms. Further details are provided in an attachment to the response[39] and are summarised below.

Study A3921044: Tofacitinib in a second line setting

Study A3921044 was a 2 year study (to correct the Delegate's statement that Study A3921044 was a 12 month study). Data from the first year of the study were available at the time of the submission (see Table 31) and 2 year data are now available and were provided with this response (Study A3921044 Month 24 CSR)[40].

Table 31: Study A3921044. Structure outcomes

	Month 6 change in mTSS† (p value vs. Placebo + MTX)	Month 6 patients with no progression in mTSS†§, % (p value vs. Placebo + MTX)	Month 12 patients with no progression in mTSS†§, % (p value vs. Placebo + MTX)
Placebo + MTX*	0.47	77.7	74.1
Tofacitinib 5 mg BD + MTX	0.12 (0.0792)	88.8 (0.0055)	86.0 (0.0050)
Tofacitinib 10 mg BD + MTX	0.06 (0.0376)	86.9 (0.0230)	86.4 (0.0034)

*Linear extrapolation beyond Month 6 because patients advanced to tofacitinib, †1-Year Analysis, §defined as change in mTSS ≤0.5 units from baseline

The mean changes from baseline with tofacitinib at both doses demonstrated continued inhibition of progression for mTSS (0.77/0.23 units in the 5 mg/10 mg groups, respectively) and for JSN through 2 years of therapy, meeting the requirements of the EMA Guidelines.

Thus, a structural benefit over 2 years was demonstrated for tofacitinib against an active comparator, strengthening validity of the assertion that tofacitinib at 5 mg (and 10 mg) bd has an effect on structure.

- Low progression

The sponsor acknowledges that at the 6 month primary time point, the change in mTSS for the 5 mg dose group compared to baseline did not meet the pre-specified criteria for statistical significance. The sponsor would like to clarify that all patients in this study, including the placebo group, received concomitant MTX, a DMARD with structure preserving properties itself. The range for the mTSS is 0-448 units (van der Heijde 2000[41]). At 6 months in Study A3921044, the mTSS had increased by 0.47/0.12/0.06 units in the placebo/5 mg/10 mg groups, respectively, indicating an extremely low rate of progression across the study population.

[39] See Fourth Round clinical evaluation report (AusPAR Attachment 4) for evaluation of these data
[40] See Fourth Round clinical evaluation report (AusPAR Attachment 4) for the clinical evaluator's assessment of this report
[41] van der Heijde D. How to Read Radiographs According to the Sharp/van der Heijde Method. J Rheumatol 2000; 27:261-3.

These changes are well below the minimal clinically important difference and smallest detectable difference of approximately 5 mTSS units measured by the van der Heijde modified method (Bruynesteyn 2002[42]). Thus, the sponsor interprets the lack of statistical significance in the primary endpoint as the result of Type II error due to the limited amount of progression in the study population, rather than due to a limited effect of the drug.

When assessing evidence for efficacy in inhibiting structural damage, it is important to consider how advances in the pharmacological management of RA have potentially impacted the clinical characteristics and natural course of disease over the past 10-15 years. In a recent analysis of TNF inhibitor clinical trials carried out over the past 16 years, Rahman et al (2011[43]) reported that since the first controlled study of a TNF inhibitor in 1993, the disease characteristics of patients enrolled in clinical studies have become less severe. The biggest change observed over time was in baseline radiographic scores, which decreased by 50% in 10 years. In addition, the actual observed radiographic progression at one year in more recent studies is lower than the estimated annual progression rates at baseline (Rahman 2011).

These observations have important implications for design and interpretation of radiographic progression as an outcome and in clinical trials powered for superiority to a control treatment (Landewe 2013[44]). In effect, the recent changes in the baseline characteristics and natural course of disease have meant that demonstrating structural superiority has become more challenging.

The sponsor notes also that ethical considerations precluded exposure of patients to placebo plus MTX for longer than 6 months without tofacitinib rescue; thus, the length of time in which placebo patients were able to demonstrate progression of structural damage (that is, an increase in mTSS) was limited. This may also have contributed to the limited progression observed in the placebo arm, with subsequent impact on the power of the study to demonstrate a statistically significant benefit from active drug (tofacitinib).

The less than expected progression in the Study A3921044 population reduces the sensitivity of the study to demonstrate robust differences between either dose of tofacitinib and placebo. While the tofacitinib 5 mg dose was not significantly different from placebo, inspection of the data and results from both pre-specified and post-hoc sensitivity analyses (referred to below) do support that both tofacitinib doses reduce the progression of joint damage in this population.

Inspection of the cumulative distribution plot indicates that the 2 values with the highest progression at 6 months are in the 5 mg dose group; these are extrapolated values from radiographs performed at 3 months. Sensitivity analyses that reduce the effect of large values (both positive and negative) all result in a statistically significant effect for 5 mg bd dose. The rank regression analysis and the proportion of non-progression analysis are two of these analyses (shown in Study A3921044 study report tables).

- Non-Progressors

[42] Bruynesteyn K, van der Heijde D, Boers M, et al. Determination of the Minimal Clinically Important Difference in Rheumatoid Arthritis Joint Damage of the Sharp/van der Heijde and Larsen/Scott Scoring Methods by Clinical Experts and Comparison With the Smallest Detectable Difference. Arthritis Rheum 2002; 46: 913-920.

[43] Rahman MU, Buchanan J, Doyle MK, et al. Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. Ann Rheum Dis 2011; 70:1631–40.

[44] Landewe R, Strand V, van der Heijde D. From inhibition of radiographic progression to maintaining structural integrity: a methodological framework for radiographic progression in rheumatoid arthritis and psoriatic arthritis clinical trials. Ann Rheum Dis 2013;72(7):1113-7.

The sponsor notes that despite the limited progression in all groups in Study A3921044, the proportion of patients with no radiographic progression (change from baseline in mTSS ≤ 0.5 units) was statistically significantly higher for both the 5 mg (86.0%, p = 0.0050) and 10 mg (86.4%, p = 0.0034) dose groups, compared to placebo (74.1%) through 12 months.

- Sensitivity analyses for high risk patients

To further examine the effect of tofacitinib as a second line therapy on structural progression, the sponsor has examined subsets of patients from Study A3921044 who had high risk of structural damage progression. These sensitivity analyses also indicate that the tofacitinib 5 mg bd dose does have a structure preserving effect. They show that tofacitinib inhibits structural damage in multiple high risk patient groups, for example, patients who are anti-cyclic citrullinated peptide (CCP)+, patients with a DAS28-4(ESR) > 5.1, seropositive patients with a baseline Erosion Score (ES) > 3, and patients with a baseline mTSS > median. A summary of these analyses was provided.

Taken together, the 2 year structural data, proportion of non-progression analysis, and sensitivity analyses in patients at high risk of structural progression from Study A3921044 confirm that both tofacitinib 5 and 10 mg inhibit structural damage in a second line setting.

The Delegate states there is *"no proven reduction in the progression of structural damage, unlike other DMARDs available"* however tofacitinib's structure modifying effects appear similar in magnitude to those reported from recent studies of a TNF inhibitor, golimumab, and an IL-6 receptor inhibitor, tocilizumab in a MTX-inadequate responder (MTX-IR, second line) population. These agents are approved in Australia as second line and first line therapies, respectively.

The sponsor notes that tofacitinib and golimumab have similar mTSS findings in the second line setting. The Australian PI for Simponi (golimumab), states *"In GOFORWARD changes from baseline in total vdH-S[45] score at week 24 in all treatment groups were minimal. No significant difference in the change from baseline in total vdH-S score at week 24 was observed in the SIMPONI + MTX groups compared with the placebo +MTX groups."* The lack of statistical significance for change in mTSS with golimumab has also been ascribed to the minimal progression seen in mTSS across the study population. Simponi (golimumab) is an approved second line therapy in Australia.

Study A3921069: Tofacitinib in a first line setting

One year data from Study A3921069 were submitted to the TGA in June 2013 during a mutual 'stop-clock' (15 May 2013 to 31 August 2013) between the sponsor and the TGA.

The 2 year CSR addendum is nearing completion and is expected to be available by 30 October 2013. The sponsor will be pleased to provide the 2 year CSR addendum to the TGA when available.

In the interim, 2 year data from Study A3921069 are provided as a manuscript submitted for peer-reviewed publication to support the positive effect of tofacitinib 5 and 10 mg in reducing the progression of radiographic structural damage and substantiate 2 year results from Study A3921044[46].

The structural preservation effect of tofacitinib is strongly supported by the results of Study A3921069, in which a highly statistically significant structural benefit compared to MTX was observed at 6, 12 and 24 months for both the 5 and 10 mg doses as monotherapy.

[45] Sharp van der Heijde Score: scoring method was first developed for scoring radiologic abnormalities in the hands and feet of patients with RA.
[46] See Fourth Round clinical evaluation report (AusPAR Attachment 4) for evaluation of this report

In this study, the progression in the MTX arm was observed to be 0.84 units at Month 6, thus indicating that there was more progression in this study population compared to what was observed in the placebo (concomitant MTX) group in Study A3921044 (0.47 units). This further supports the hypothesis that the statistical significance of the results in Study A3921044 was impacted by the low progression of the study population, and not the effectiveness of tofacitinib.

The 2 year data show a change in mTSS of 2.08/0.55/0.28 units for the MTX/5 mg/10 mg groups, respectively. The mTSS results for the 5 mg and 10 mg dose groups remained highly statistically significant compared to MTX ($p < 0.001$) at 2 years, as were the JSN and ES (both components of the mTSS).

Prior to this study, no medication, in a single head-to-head trial, has been shown to be more effective both clinically and structurally compared to MTX, the most widely used first line therapy in RA. It confirms a structural benefit for tofacitinib at both the 5 and 10 mg doses through 2 years, meeting the requirements of the EMA Guidelines adopted by the TGA.

Effect on inflammatory markers

The Delegate makes several references to tofacitinib not having a significant effect on inflammatory markers:

- *"An improvement in inflammatory markers was seen with both doses levels [sic] of tofacitinib compared with methotrexate but this was not significant",*
- *"there was no significant alteration of the ESR compared with placebo raising a concern as to whether the underlying inflammatory process was being significantly limited at this dose", and*
- *"neither the 5 mg or 10 mg dose levels demonstrated a significant effect on serum inflammatory markers which raises some uncertainty about whether the underlying inflammatory process is being controlled,"*

as well as the seemingly contradictory statement that *"when used in combination with other DMARDs, the addition of 5 mg twice daily tofacitinib significantly improved the clinical signs and symptoms and inflammatory markers compared with placebo."*

Clinically and statistically significant reductions in acute phase reactant inflammatory markers, that is CRP and erythrocyte sedimentation rate (ESR), were observed at both tofacitinib doses in all treatment settings studied (as monotherapy compared to placebo in Study A3921045, as monotherapy compared to MTX in Study A3921069, with concomitant MTX compared to MTX alone in Studies A3921032, A3921044 and A3921064, and with concomitant DMARDs compared to DMARDs alone in Study A3921046). The three month time point was selected for this table because the control group treatment was "as assigned", that is, prior to any placebo patient advancing to tofacitinib treatment.

These data consistently demonstrate that tofacitinib at both the 5 and 10 mg dose levels have a statistically significant effect on inflammatory markers compared to placebo or MTX, providing clear evidence that the underlying disease process is being controlled.

The basis for the Delegate's statements questioning the favourable effect of tofacitinib (either as monotherapy or in combination) on inflammatory marker levels is therefore unclear.

Efficacy conclusion

Two year results from Study A3921044 indicate the continued inhibition of structural progression for the 5 mg bd dose, as measured by mTSS and JSN. The sensitivity analyses in this study confirm that the 5 mg bd dose does have a structure preserving effect. This

conclusion is strongly supported by the results from the A3921069 trial, in which a highly statistically significant and robust effect was observed at both the 5 and 10 mg bd doses through 2 years. The overall effect of tofacitinib in inhibiting structural damage is consistent with that seen in recent studies of biologic agents, including TNF inhibitor agents, and has now been demonstrated over 2 years, as required by the EMA guidelines.

In general, the structural efficacy of tofacitinib appears not dissimilar to that of golimumab (Simponi Australian PI), a biologic DMARD approved as a second line therapy, which (in combination with MTX) demonstrated statistically significant structural benefit in a MTX-naïve, first line population (GO-BEFORE study) but did not demonstrate statistical significance for change in mTSS in a MTX-IR, second line population (GO-FORWARD study), due to limited structural progression observed in all treatment groups.

Data also clearly demonstrate that tofacitinib at both 5 and 10 mg dose levels has a clinically meaningful and statistically significant effect on inflammatory markers, confirming that the underlying RA disease process is being controlled.

Study program and study design considerations

The sponsor wishes to address several comments by the Delegate regarding specific aspects of study design.

The Delegate states *"The studies conducted were adequately powered to detect the differences being examined in each study. They included adequate number of patients, although in some studies, the number completing placebo or control treatments were low, with those dropping out being classified thereafter as non-responders, which would potentially bias towards finding an effect in favour of the study drug."*

In the 5 placebo controlled Phase III studies, 2 were 1 year studies (Studies A3921046 and A3921064), one was 2 years with a 1 year interim report (Study A3921044) and the other two were 6 months in duration (Studies A3921032 and A3921045). The 6 month studies assessed all primary endpoints at 3 months and advanced all placebo patients to active treatment (tofacitinib, 5 or 10 mg bd) at that time. The 3 other studies assessed primary endpoints at 6 months (excepting Health Assessment Questionnaire-Disability Index (HAQDI), which was assessed at 3 months) and included advancement or "early escape" of placebo patients at Month 3 if they had less than a 20% improvement from baseline in swollen and tender joint counts; all remaining placebo patients were advanced to tofacitinib at 6 months.

In order to ensure an unbiased comparison of tofacitinib to placebo in the 1-2 year studies, all patients who were advanced at Month 3, regardless of randomised treatment, were considered as non-responders for dichotomous primary (ACR20, DAS28-4 (ESR) < 2.6) and many secondary endpoints (for example, ACR50, ACR70, DAS28-4(ESR) ≤ 3.2). For the 6 month studies, the primary endpoints were assessed at 3 months, prior to any advancement.

The sponsor wishes to emphasise that all patients, placebo and tofacitinib, who dropped out prior to the analysis time point were considered non-responders. This is a typical conservative approach that requires patients to have sufficient improvement in signs and symptoms and to stay on their assigned therapy for the required time to be considered a responder. Since all treatment arms are treated in the same manner for comparative analysis, there is no bias due to this primary analysis methodology. The non-responder imputation method used in the tofacitinib program is consistent with that used in recent trials of bDMARDs approved in Australia (for example, Emery 2008, Keystone 2008, Kremer 2011).

The Delegate comments *"As there was no direct comparison with a TNF alpha inhibitor to demonstrate superiority, or non-inferiority, only inferences of the relative efficacy of tofacitinib compared with adalimumab can be made, and its role as a second line therapy*

has not been adequately demonstrated." The TGA adopted EMA guidance CHMP/EWP/556/95 rev 1 *Points to Consider on Clinical Investigation of Medicinal Products Other than NSAIDs for Treatment of Rheumatoid Arthritis* does not require a superiority or non-inferiority direct comparison against a TNFα inhibitor to be performed. The efficacy and safety of tofacitinib has been investigated in 4260 patients having an inadequate response to DMARD therapy at baseline. Thus, its role as a second line agent has been extensively studied, compared to both placebo and active DMARD comparators.

To the sponsor's knowledge, none of the 8 bDMARDs currently approved by the TGA (adalimumab, etanercept, infliximab, certolizumab, golimumab, abatacept, tocilizumab, rituximab) had been evaluated in a superiority or non-inferiority direct comparison against a TNFα inhibitor at time of registration. Nevertheless, 5 of these therapies have received first line indications from the TGA (Humira, Enbrel, Remicade, Orencia and Actemra Australian PIs), 2 have received second line indications (Cimzia and Simponi Australian PIs) and only 1 has received a third line indication (Mabthera Australian PI), indicating that lack of such a direct comparison study has not been a requirement for TGA approval as a first or second line therapy in the past.

The Delegate's states that *"There need to be longer term data (minimum 24 months) presented for the mTSS in those on tofacitinib versus placebo to determine whether there is any structural benefit with tofacitinib with either the 5 mg or 10 mg dose levels." However the EMA Guidelines state "Since it would be unethical to retain a patient with RA on placebo treatment indefinitely, the duration of placebo control must necessarily be limited. Depending on the severity and the activity of the disease three to six months is acceptable."*

The EMA has recognised that ethical considerations limit the duration of placebo control and accepted a primary analysis time point for mTSS at 6 months, prior to initiation of the Phase III program. This requirement for a limited duration for placebo is also noted in the current FDA guidelines (*Draft guidance for industry and FDA staff: Rheumatoid Arthritis: Developing Drug Products for Treatment*, 2013).

Medical need for a second line therapy

The use of traditional and biologic DMARDs has resulted in significant improvements in outcomes for patients with RA. However, despite the availability of multiple therapeutic options, many patients fail to adequately respond to treatment or stop responding over time and there is no reliable way to predict which patients will respond to a given agent (Kavanaugh 2004). The majority of patients on non-biologic DMARDs alone are unable to achieve adequate control of their disease (Lambert 2004, Kremer 2001). While MTX remains the cornerstone of RA treatment, many patients have an inadequate response or are intolerant to MTX alone or in combination with other DMARDs (Russell 2010). While the biologic agents have represented a major treatment advance, no single agent is effective in all patients and loss of efficacy and poor patient tolerability frequently lead to treatment discontinuation (Kavanaugh 2004, Markenson 2011, Greenberg 2012).

Typically, biologic DMARDs are prescribed with MTX because a better response is attained with the combination compared to either agent alone (Bykerk 2012, Russell 2010). Additional treatment options that are effective and well tolerated as a monotherapy for the treatment of moderate to severe RA are needed for those patients for which MTX is contraindicated or not well tolerated, or when adherence to concomitant DMARD therapy is not optimal.

The biologic DMARDs currently available are all administered parenterally. This mode of administration introduces adverse events not associated with orally administered medications: feelings of discomfort, erythema, pruritis, pyrexia, induration, pain, oedema or itching (Murdaca 2013). Additionally, many people are not comfortable with or are afraid of injections, and patients may experience fear and anxiety about starting a new

therapy that involves regular injection/infusions, potentially delaying their willingness to initiate treatment.

Due to their physical properties all biologics have the potential to elicit an immune response or immunogenicity in humans (Strand 2007). This immune response stimulates the production of anti-drug antibodies, which can result in enhanced clearance/reduced drug levels and/or therapeutic drug inactivation and is a particular issue for therapeutic monoclonal antibodies such as adalimumab (Wolbink 2009, Krieckaert 2010). Tofacitinib is a small molecule chemical DMARD, not a bDMARD (contrary to the statement in the Delegate's Overview stating that tofacitinib represents *"the first time an oral bDMARD has been proposed for use in RA"*). Thus, many of the considerations that affect biologic DMARDs, such as parenteral administration and immunogenicity, do not apply to tofacitinib.

Hence, there remain substantial unmet medical needs for additional therapeutic options with different mechanisms of action, oral route of administration, demonstrated efficacy especially as monotherapy and sustained responses not affected by immunogenicity, to meet treatment goals throughout the course of this chronic, lifelong disease in patients who have had an inadequate response or are intolerant to MTX.

Conclusions

The sponsor proposes that on the basis of the available evidence, tofacitinib 5 mg bd should be approved as a second line therapy. The sponsor has shown that:

- Tofacitinib has been studied extensively and predominantly in a second line setting
- Clinical efficacy has been demonstrated in the second line therapy setting and is comparable to adalimumab (as stated by the Delegate), which is approved in Australia as a first line therapy
- Structural efficacy has been demonstrated and is similar to golimumab, which is approved in Australia as a second line therapy
- Structure preservation efficacy has been demonstrated over 2 years as per the EMA Guidelines adopted by the TGA, and for both first and second line populations.
- Tofacitinib has a robust effect on inflammatory markers, showing the underlying inflammatory process is being controlled
- Concern about dose dependent increase in AEs has been addressed by withdrawal of the sponsor's application for registration of the 10 mg dose
- The rate and type of AEs seen with the 5 mg bd dose are comparable to that seen with biologic DMARDs approved in Australia as first or second line therapies
- The sponsor's agreement to restrict prescribing to rheumatologists and specialist physicians with expertise in the management of RA, ensures treatment will be initiated and managed by healthcare professionals well familiar with the adverse event profile of tofacitinib through their experience with use of biologic DMARDs
- Convincing evidence has been provided that tofacitinib treatment is not associated with an increase in the potential torsadogenic (that is, pro-arrhythmic) risk.
- An extensive RMP including educational program will mitigate the risks associated with an immunomodulatory therapy such as tofacitinib and ensure the safe and appropriate use of tofacitinib.

The sponsor has previously noted the favourable first and second round clinical assessments of the benefit-risk balance for tofacitinib given the proposed usage (as a

second line therapy), and the additional efficacy outcomes and absence of any new safety issues identified in the Third round assessment of benefits and risks.

The basis for the Delegate justifying consideration of tofacitinib for use in a third line setting only, such as the purported lack of demonstration of structural benefit and purported lack of effect on inflammatory markers, is refuted by the weight of evidence for tofacitinib 5 mg bd in both first and second line populations. The sponsor continues to maintain, based on the totality of the available information, that tofacitinib has a favourable benefit-risk profile as a second line therapy at the 5 mg dose.

Tofacitinib will provide an additional therapeutic option with a unique mechanism of action, oral route of administration, proven efficacy and manageable safety profile for patients with moderate to severe active RA who have had inadequate response to or are intolerant to previous DMARD therapy. These treatment-refractory patients require new treatment options with novel mechanisms of action.

VI. Clinical findings fourth round

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 4 (Fourth round CER).

Introduction

This is a supplementary CER to assess the additional data submitted by the sponsor in the sponsor's response to the Delegates' initial Overview and Addendum, including the specific questions to the sponsor contained in these documents.

The sponsor's initial proposed indication was:

> *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. Xeljanz can be used alone or in combination with DMARDS, including methotrexate.*

Following the Third round CER and receipt of the Delegate's Overview, the sponsor amended the proposed indication to:

> *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. Xeljanz can be used alone or in combination with non-biological DMARDS, including methotrexate. Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

The submission initially proposed registration of 5 mg and 10 mg tablets. The sponsor now intended to proceed with registration of the 5 mg dose form only.

Contents of the clinical dossier

The additional data comprised:

- Response from the sponsor
- Supporting attachments
- Manuscript describing data from year 2 of Study A3921069
- Year 2 report from Study A3921044

- Individual patient data for subjects with QTc prolongation from Study A3921069.
- Summaries of ECG changes for Study A3921019, Study A3921025, Study A3921035, Study A3921039, Study A3921040, and Study A3921045.
- Summaries of abnormal ECGs by visit for Study A3921019, Study A3921025, Study A3921035, Study A3921039, Study A3921040, and Study A3921045.
- Summaries of abnormal ECGs from monotherapy studies for up to 3 months.
- Summary table of subjects with Torsades de pointes.

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.

Efficacy

Studies providing efficacy data

Efficacy in comparison with MTX

- A manuscript submitted to a medical journal reporting the Year 2 results for Study A3921069 was provided.
- An updated study report describing the Year 2 data for Study A3921044 was provided.

Findings from these studies are discussed under *Fourth round evaluation of clinical data submitted in response to Round 3 questions*, below.

Safety

Studies providing evaluable safety data

- Individual patient data for subjects with QTc prolongation were provided for Study A3921069.
- Safety data were provided for Year 2 for Study A3921044.
- Summaries of ECG changes for Study A3921019, Study A3921025, Study A3921035, Study A3921039, Study A3921040, and Study A3921045.
- Summaries of abnormal ECGs by visit for Study A3921019, Study A3921025, Study A3921035, Study A3921039, Study A3921040, and Study A3921045.
- Summaries of abnormal ECGs from monotherapy studies for up to 3 months.
- Summary table of subjects with Torsades de pointes.

Findings from these studies are discussed under *Fourth round evaluation of clinical data submitted in response to Round 3 questions,* below.

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.

Fourth round evaluation of clinical data submitted in response to Delegate's questions

The sponsor provided further data and opinion in response to the concerns regarding QTc prolongation; data in support of an effect on structural progression; and data in support of an indication as second line treatment.

QTc prolongation

With regard the concerns of QTc prolongation, the sponsor provided a response consisting of a general review of QTc prolongation and, presumably, expert opinion, although authorship of the document is not attributed (see AusPAR Attachment 4 for full details of the response).

The sponsor also provided summary tabulations of the mean increase in QTcF from baseline to final visit, by study, for the development and number and proportion of subjects with increase in QTcF ≥ 60 msec. These tabulations indicate no issues with the studies of shorter duration (up to 24 weeks) but in studies of 6 months or longer there were some increases in mean QTcF and in the proportions of subjects with increase in QTcF ≥ 60 msec. These changes are no worse than those observed with MTX. Although this is not a clear indication that tofacitinib is associated with prolongation of the QT interval, the possibility that these observations could represent a cumulative toxicity cannot be discounted and has not been addressed in the sponsor's response.

Evaluation of responses to additional Round 3 questions

The clinical evaluator's assessment of the sponsor responses to questions that were raised by the Delegate in relation to the findings from Study A3921069 (see Addendum to Delegate's initial Overview, above) is as follows:

TGA question 1

These data were provided for the subject. The noteworthy concurrent medications were hydroxychloroquine and amitriptyline. No drug interactions are anticipated with these agents. No other AEs, relevant laboratory abnormalities, including abnormal liver function tests or renal impairment, occurred at the time of the AE. The patient did not have a history of any additional factors for QT prolongation. QTcF was 428 msec on Day -28, 517 msec on Day 351, 433 msec on Day 371 and 456 msec on Day 791. The subject is reported to be continuing to take tofacitinib 10 mg bd.

TGA question 2

The sponsor advised that: "*A total of 8 patients had screening QTcF values ≥ 500 msec: 3 patients each in the tofacitinib 5 mg and 10 mg groups, and 2 patients in the methotrexate group. All 8 patients received treatment.*" The following data were provided for these subjects:

Table 32: Screening QTcF values ≥ 500 msec. Study A3921069

Treatment	QTcF Interval (Fridericia's Correction) (msec)			Total Days of Dosing in A3921069
	Screening	Year 1	Year 2	
CP-690,550 5mg BID	503	NA	NA	371
CP-690,550 5mg BID	536	390	NA	252
CP-690,550 5mg BID	500	not calculated	not calculated	716
CP-690,550 10mg BID	502	437	459	721
CP-690,550 10mg BID	670	456	NA	441
CP-690,550 10mg BID	541	507	464	440
Methotrexate	520	484	450	714
Methotrexate	526	411	424	728

Note: this table has been modified from the original to remove patient identifier details.

None of the subjects with available data had QTcF ≥ 500 msec post-screening.

TGA question 3

Only one of the eight subjects with QTc > 500 msec had a baseline recording of > 500 msec. The sponsor provided a summary tabulation of QTcF at baseline, Year 1 and Year 2. None of the subjects had QTcF > 500 msec at Year 2.

TGA question 4

A total of 16 patients with Baseline QTcF values < 500 msec had at least one treatment emergent QTcF measurement ≥ 500 msec after receiving tofacitinib; 8 each in the 10 mg and 5 mg treatment groups. Seven of these subjects had the elevated value at Year 1, and 9 subjects had the elevated value at Year 2 (or early termination). None had a QTcF value ≥ 500 msec at 2 consecutive visits.

The following summary tabulation was provided:

Table 33: Patients with QTc >500 msec while on either dose of tofacitinib. Study A3921069

Treatment	QTcF		
	Pre-Study	Year 1	Year 2 or ET
CP-690,550 5mg BID	405	NA	560*
CP-690,550 5mg BID	434	NA	503*
CP-690,550 5mg BID	400	500	424
CP-690,550 5mg BID	450	402/663†	420
CP-690,550 5mg BID	484	539	451
CP-690,550 5mg BID	451	529	435
CP-690,550 5mg BID	457	520	431
CP-690,550 5mg BID	393	NA	510*
CP-690,550 10mg BID	457	413	4520**
CP-690,550 10mg BID	406	684	422
CP-690,550 10mg BID	444	510	413
CP-690,550 10mg BID	446	432	534
CP-690,550 10mg BID	372	NA	810*
CP-690,550 10mg BID	403	486	534
CP-690,550 10mg BID	414	408	557
CP-690,550 10mg BID	452	391	517

† The 2nd QTcF value at Year 1 (663 msec) was obtained at an unplanned visit within the Year 1 window.
* QTcF value obtained at early termination visit which occurred at or prior to Month 12.
** RR interval recorded as 1 for this patient at the Year 2 visit ECG. QT interval and heart rate (RR interval calculated from heart rate) at the Baseline, Year 1 and Year 2 visits were 444, 423, and 452 msec and 52 (1154 msec), 55 (1091 msec), and 54 (1111 msec) bpm respectively. The corrected QTcF using the Fridericia formula at Baseline, Year 1 and Year 2 visits were 423, 411, and 436 msec respectively.
RR intervals calculated as 60,000 msec/HR in bpm. QTcF calculated as QT/[cube root of(RR interval in seconds)]
Abbreviations: NA, not applicable.; ET, early termination

Note: this table has been modified from the original to remove patient identifier details.

The QTcF of 4520 msec for one subject is presumed to be a typographical error but requires clarification by the sponsor. The QTcF of 810 msec for another subject could represent a typographical or a data entry error and also requires clarification by the sponsor.

Drugs known to affect QT interval were taken by six of the nine patients. Chloroquine or hydroxychloroquine were taken throughout the study by three patients; Bactrim (sulfamethoxazole/trimethoprim) was taken from Day 713-722 by one patient, ofloxacin from Days 178-182 and 633 to 637 by one patient, and mirtazapine daily regimen was started on Day 451 for one patient. In the evaluator's opinion, these concomitant medications could have been responsible for the QTc prolongation in these subjects.

None of these subjects discontinued because of QT prolongation.

TGA question 5

Two subjects (one subject in the tofacitinib 5 mg bd group and the other in the MTX group) reported a QTcF increase of ≥ 60 msec in an unplanned reading but were not included in the ECG summary since the unplanned result was not the last value recorded prior to a visit.

For the first subject, QTcF was 419 msec on Day -28, 483 msec on Day 351, 422 msec on Day 371 and 455 msec on Day 719. For the other subject, QTcF was 375 msec on Day -27, 441 msec on Day 85 and 417 msec on Day 99.

TGA question 6

The sponsor has provided a tabulation of concomitant medications that may have contributed to QT prolongation. A significant number of the QT prolongation events may have been contributed to by these concomitant medications. The sponsor also provided a tabulation of subjects with impairment of hepatic or renal function who also had QT prolongation. Ten subjects who developed QTcF ≥ 500 msec or an increase in QTcF ≥ 60 msec reported AEs associated with changes in renal or hepatic function during their participation in the study: four subjects each in the tofacitinib 5 mg and 10 mg bd groups, and two in the MTX group.

TGA question 7

A summary of the 24 month ECG data for Study A3921069 is available and was provided in an attachment to the sponsor response. The mean (95% CI) change from baseline in QTcF was 4.7 (1.9 to 7.5) msec for the 5 mg dose level, 18.3 (-1.7 to 38.3) msec for the 10 mg and 30.1 (-10.9 to 71.1) msec for MTX. The number (%) of subjects with an increase in QTcF from baseline ≥ 60 msec was 16 (4.7%) subjects for the 5 mg dose, 19 (5.4%) for the 10 mg and nine (5.5%) for the MTX dose. These data do not raise any additional safety concerns.

TGA question 8

None of the subjects with prolongation of QT discontinued for that reason, but three in the tofacitinib groups discontinued because of increased serum creatinine.

TGA question 9

Summary ECG tables were not generated in the 1 year CSR as Study A3921069 was an ongoing study at the time of this CSR, and there was no evidence that tofacitinib was associated with a prolongation of the QTc interval or an increase in the potential pro-arrhythmic risk in the completed nonclinical and clinical studies within the large tofacitinib RA program.

In the evaluator's opinion, as the ECG data were collected as a safety outcome measure for Study A3921069, these data would be expected to be included in any interim report submitted in support of efficacy and safety. The sponsor should have been aware of the concern that the results of the QTc would have caused and should have addressed these in the study report.

TGA question 10

A summary of the ECG data from other pivotal efficacy studies was provided in an attachment to the sponsor response. The 24 month ECG data from Study A3921044 is not summarised in the tables. For Study A3921045, at Month 6, the number (%) of subjects with an increase in QTcF from baseline ≥ 60 msec was eleven (4.9%) for the 5 mg dose, nine (4.0%) for the 10 mg dose, one (1.8%) for the placebo to 5 mg group and one (1.8%) for the placebo to 10 mg group. These data do not raise any additional safety concerns.

TGA question 11

A post-hoc analysis of the ECG data across the clinical program was provided in an attachment to the sponsor response and includes ECG data up to Month 24 from Study A3921069. The ECG data from Study A3921044 were not included. These data do not raise any additional safety concerns.

TGA question 12

The sponsor performed a search for any cases with reported fatal outcome that were received by Pfizer prior to 9 September 2013 in the combined data sets of the tofacitinib RA Phase II, Phase III, and long term extension studies. A total of 13 cases of sudden death that were possibly attributed to cardiac disorders were identified. After review, two cases

were excluded, including one case with the event of death which occurred during the pre-randomisation phase prior to treatment with study drug and one case where the patient was treated with adalimumab 40 mg every two weeks. The characteristics and descriptions of the remaining 11 cases were presented. All of these subjects appear to have underlying medical conditions that would have contributed to sudden death.

Issues raised in the delegate's initial overview

Post-hoc sensitivity analysis: joint progression

The sponsor provided a post-hoc sensitivity analysis in order to demonstrate that the lack of a significant finding for an effect on joint progression in Study A3921044 was due to a low progression rate in the study population. These analyses involved a considerable amount of data manipulation, simulation (estimation) of data and imputation of missing variables. It is not clear from the description of the study how many actual observations have been excluded from the analysis and how many new observations have been created. It was not clear to the evaluator what the objective of the study was, whether the investigators were working to a predetermined sequence of analyses, and whether the methods of analyses were determined before the study was commenced, or during the study.

In the opinion of the evaluator, these types of analyses might be useful in the design of Phase III studies, provided the assumptions used in the study are carefully scrutinised for plausibility, but are not evaluable for efficacy. The sponsor also implies that Study A3921044 lacked the statistical power to demonstrate a significant effect on progression. Whilst the evaluator agrees that Study A3921044 was underpowered, it is a convoluted argument to interpret this lack of power as supporting efficacy.

Efficacy with regard to structural progression

In support of the claim of efficacy with regard to structural progression the sponsor has submitted further data in the form of a manuscript submitted to a scientific journal for publication. The manuscript reports the 2 year results for Study A3921069 and clearly has been prepared at the direction of the sponsor. In the opinion of the evaluator, the methods and results are not reported in sufficient detail for the report to be evaluable in support of efficacy or safety. It is not stated how missing data were imputed and how many subjects in each treatment group were included in the analysis of efficacy at each time point. The safety data are incomplete and do not include any discussion of ECGs, one of the major issues identified in the current application. Although the tabulations of efficacy data included in the manuscript are of interest, and promising of efficacy, it is not possible for the evaluator to interpret the results without being aware of the methods used to impute missing data, and the numbers of subjects included in the analysis.

The limitations section does bring up the interesting issue that the dose of MTX could not be adjusted during the study, which draws attention to the emerging use of therapeutic drug monitoring (MTX-polyglutamates) to refine treatment with MTX leading to better efficacy and safety. Hence the comparator treatment with MTX may not have represented best practice.

Relevance of structural findings in the context of the proposed second line indication

In another attachment the sponsor has provided an argument (in the form of expert opinion) that because of the mechanism of action of tofacitinib it would be expected to have an effect on progression. The last sentence of this report states: *The sponsor has provided 2 year data from Study A3921069 (tofacitinib as a first line therapy) to support the positive effect of tofacitinib in reducing the progression of radiographic structural damage and substantiate 2 year results from Study A3921044 (tofacitinib as a second line therapy).*

The 1 year data for Study A3921044 did not demonstrate efficacy for progression for the 5 mg dose level. The two year results for Study A3921044 were provided in the dossier. Study A3921044 was placebo controlled to Month 6, then was a comparison of the 5 mg and 10 mg dose levels. There were 402 subjects allocated to the 5 mg dose level and 398 to the 10 mg. These data indicate no difference in progression between the 5 mg and 10 mg dose levels, but do not enable comparison with placebo. Hence, in Study A3921044 neither the 5 mg nor the 10 mg dose levels have been demonstrated to have efficacy at 2 years with regards progression. The study was never intended to demonstrate efficacy at 24 months as no such analysis is in the statistical analysis plan. There is therefore nothing to substantiate[47].

The 2 year results for Study A3921069 have not been provided in sufficient detail for analysis, as discussed above. Hence, these data are not able to substantiate 2 year results from another study.

Hence, the sponsor's claims of efficacy for the two year data are not supported by the data submitted.

In addition, in the opinion of the evaluator, the approved indication should be consistent with the benefit-risk balance and not just reflect the efficacy data alone.

Meta-analysis in support of safety

In their response the sponsor has referred to a meta-analysis that they conducted in support of safety. The meta-analysis is purported to indicate that tofacitinib has a similar rate of serious infections, herpes zoster and malignancy as bDMARDs. Although the sponsor has provided tabulations and figures that demonstrate this in their response, and a description of the methodology for the study, the evaluator was not able to locate the report of this meta-analysis.

Clinical evaluator's follow-up questions

A further four questions were submitted to the sponsor in order to clarify aspects of the Fourth round data, above:

TGA question: Please provide an update on the outcome (or end of study report, if this study has been completed) of Study A3921152 which addresses renal function while on tofacitinib. If these data are not available, please state when this study was commenced and its completion date, and the planned timing of any interim reports.

The sponsor responded that Study A3921152 has completed last subject/last visit, but the final CSR is in progress and not yet completed. A presentation of data from three other previous studies was provided in poster format. Over 3 months, serum creatinine concentration increased by 0.07 mg/dL and 0.08 mg/dL with tofacitinib 5 mg bd and 10 mg bd. Increases in serum creatinine of 0.04 mg/dL in the placebo group and 0.06 mg/dL in the adalimumab groups were observed. The changes in serum creatinine correlated with CRP at baseline. There were insufficient data to conclude whether the changes in serum creatinine reflected worsening renal function, or improved muscle mass. The results of Study A3921152 may clarify this issue.

TGA question: The QTcF is reported as 4520 msec for a subject. Please could the sponsor clarify whether this is a typographical error and provide the QTcF result.

The value of 4520 msec resulted from a data entry error, the recalculated QTcF value at Year 2 was 436 msec.

[47] Sponsor clarification: Study A3921044 included endpoints that describe efficacy at Month 24 but there was no planned comparison to placebo at Month 24 due to ethical barriers to keeping patients on placebo for a prolonged period.

TGA question: The QTcF of 810 msec for a subject. Please could the sponsor clarify if this is a typographical and if so, the actual QTcF result.

The value of 810 msec resulted from a data entry error, the recalculated QTcF value was 388 msec.

TGA question: According to the protocol for Study A3921044 ECGs were to be performed at 24 months or at the end of the study. The efficacy data were submitted for evaluation but the ECG data are not included in the study report. Please provide these ECG data.

The sponsor provided qualitative data only for Study A3921044 and did not provide analysis of QTc interval data. The qualitative data provided by the sponsor may be incomplete and included a number of typographical errors. The following data were extracted from the listing:

- A subject had QT prolongation at baseline and at Day 716
- A subject had QT prolongation at baseline and QT interval "alongation" on Day 722
- A subject had a prolonged QT interval at Day 365 that was not reported at baseline
- A subject had a prolonged QT interval noted on Day 380, Day 385 and Day 387
- A subject had prolonged QT noted at baseline
- A subject had slight QT prolongation at Day 283
- A subject had QT prolongation noted at Day 357 and QT "allongation" at Day 730
- A subject had QT "prolougel" at Day 722
- A subject had "longered" QTc at baseline.

The data were incomplete and in the opinion of the evaluator no conclusions can be drawn from them.

Fourth round benefit-risk assessment

Fourth round assessment of benefits

After consideration of the responses to clinical questions, the benefits of tofacitinib in the proposed usage are unchanged from the *Third round assessment of benefits* (above).

Although clinical benefit for the 5 mg bd dose level has been demonstrated for tofacitinib, the data are not sufficient to demonstrate joint preservation.

Fourth round assessment of risks

After consideration of the responses to clinical questions, the benefits of tofactinib in the proposed usage are unchanged from the Third round evaluation as stated in the *Third round assessment of risks* (above).

The risk of QTc prolongation is not sufficient to preclude authorisation, but would be sufficient to be included in the RMP as an important potential risk. The risks of infection and malignancy appear to be similar to those for bDMARDs.

Fourth round assessment of benefit-risk balance

The benefit-risk balance is unchanged from the *Third round assessment of benefit-risk balance* (above).

The evaluator understands the proposed usage to be in the patient population that has no alternative treatment available (that is, has failed treatment with either biological and non-biological DMARDs or where these agents are contraindicated). This understanding is based on:

- In the Third round evaluation, the sponsor was prepared to accept a third line indication for tofacitinib.
- The sponsor has also been prepared to modify the indication in Europe and has stated: "*While Pfizer continues to believe that the preponderance of evidence supports use of tofacitinib as a second line therapy, the indication was modified specifically for the marketing authorisation application (MAA) in Europe based on feedback received during the review process and in an attempt to find a conservative, compromise position that would make tofacitinib initially available only to "third line" European RA patients with higher unmet medical need than "second line" patients.*"

Hence, the benefit-risk balance of tofacitinib, given the proposed third line usage, is favourable.

Fourth round recommendation regarding authorisation

The clinical evaluator is unable to recommend approval of the submission with the indication as proposed:

> *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. Xeljanz can be used alone or in combination with non-biological DMARDS, including methotrexate. Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

The proposed indication does not reflect the status of tofacitinib as a third line agent[48].

The clinical evaluator would be able to recommend approval of the submission with the following amended indication:

> *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. Xeljanz can be used alone or in combination with DMARDS, including methotrexate. Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 1.0 dated 27 September 2011 [Data lock point 29MAR2011] with Australian Specific Annex (ASA) and, later, EU-RMP Version 1.1 dated 04 September 2012 [Data lock point 29SEP2011] with ASA, which were reviewed by the TGA's Office of Product Review (OPR).

[48] In response to the Fourth round clinical evaluation report, the sponsor clarified that it had not changed its position in the Australian application that a second line indication is the most appropriate for Xeljanz, based on the scope of the development program and the demonstration of a favourable benefit:risk in RA patients in second line therapy.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 34.

Table 34: Summary of ongoing safety concerns

Important identified risks	Serious and other Important Infections
	Decrease in neutrophil count and neutropenia
	Decreases in lymphocyte count and lymphopenia
	Decrease in haemoglobin levels and anaemia
	Lipid elevations and hyperlipidaemia
Important potential risks	Malignancy including lymphoma
	Cardiovascular risk
	Gastrointestinal perforation
	Transaminase increases and potential for drug induced liver injury
Important missing information	Effects on pregnancy and the fetus
	Use in breastfeeding
	Effect on Vaccination Efficacy and the Use of Live/Attenuated Vaccines with tofacitinib
	Use in paediatric patients
	Use in Combination with other rheumatoid arthritis therapies
	Use in severe hepatic impairment
	Use in mild or moderate hepatic impairment
	Use in severe renal impairment
	Use in moderate renal impairment
	Use in Patients with Evidence of Hepatitis B or C infections
	Use in patients with elevated transaminases

Pharmacovigilance plan

Routine and additional pharmacovigilance activities are proposed by the sponsor to monitor the ongoing safety concerns associated with tofacitinib. Ongoing and planned additional pharmacovigilance studies are summarised in the table below.

Table 35: Additional pharmacovigilance activity

Additional pharmacovigilance activity	Assigned safety concerns	Status
Australian Rheumatology Association Database (ARAD)	Long term safety (unassigned as ARAD is independent database) Malignancies (unassigned as ARAD is independent database)	Planned
Active surveillance utilising one US registry and 3 European registries for a minimum of 5 years	Serious and other important infections Malignancy including lymphoma GI perforation Cardiovascular Risk	Planned
Active surveillance utilising Organization of Teratology Information Specialists (OTIS) for a minimum of 5 years	Effects on pregnancy and the fetus	Planned
Retrospective cohort study using a US registry	Cardiovascular risk	Planned
Paediatric investigational plan: A3921103: Pharmacokinetics A3921104: Juvenile Idiopathic Arthritis A3921165: Systemic JIA with active systemic features A3921145: Extension study.	Use in paediatric patients	Planned
Continuation of the long term extension studies A3921024 and A3921041 for a minimum of 2 years post approval.	Serious and other important infections Malignancy including lymphoma GI perforation Cardiovascular Risk	Ongoing (both studies)
A3921129 Vaccine sub-study included in study A3921024	Effect on vaccination efficacy Use of live/attenuated vaccines	Ongoing

Risk minimisation activities

The sponsor's conclusions in regard to the need for risk minimisation activities are shown in Table 36.

Table 36: Sponsor conclusions on the need for risk minimisation activities

Ongoing safety concerns	Routine risk minimisation sufficient?	If yes, justification provided by sponsor
Important identified risks		
Serious and other Important Infections	No	
Decrease in neutrophil count and neutropenia	No	
Decreases in lymphocyte count and lymphopenia	No	
Decrease in haemoglobin levels and anaemia	Yes	Clinically relevant anaemia associated with tofacitinib is infrequent and product labelling addresses the risk appropriately.
Lipid elevations and hyperlipidaemia	No	
Important potential risks		
Malignancy including lymphoma	No	
Cardiovascular risk	Yes	Lipid elevations are of important primarily due to their use as a CV risk factor. An increase in CV risk has not been identified in tofacitinib treated RA patients; assessment of potential risk is ongoing.
Gastrointestinal perforation	No	
Transaminase increases and potential for drug induced liver injury	Yes	Clinically important increases in transaminases associated with tofacitinib not often observed; product labelling addresses the risk appropriately

Ongoing safety concerns	Routine risk minimisation sufficient?	If yes, justification provided by sponsor
Important missing information		
Effects on pregnancy and the fetus	No	
Use in breastfeeding	Yes	Data are not available on the safety of tofacitinib use during pregnancy
Effect on Vaccination Efficacy and the Use of Live/Attenuated Vaccines with tofacitinib	No	
Use in paediatric patients	Yes	Data are not available on the safety and efficacy of tofacitinib in patients <18 years of age. Assessment of this population is planned.
Use in Combination with other rheumatoid arthritis therapies	Yes	Data are not available on the combined use of tofacitinib with biologic DMARDS and other biologic RA therapies. The label appropriately warns against such use.
Use in severe hepatic impairment	Yes	
Use in mild or moderate hepatic impairment	Yes	
Use in severe renal impairment	Yes	
Use in moderate renal impairment	Yes	
Use in Patients with Evidence of Hepatitis B or C infections	Yes	
Use in patients with elevated transaminases	Yes	

Risk minimisation plan

The sponsor proposes a plan to implement a number of prescriber and patient educational activities following the registration of tofacitinib in Australia including the following educational activities:

- letter to all Australian rheumatologists advising of the regulatory approval of tofacitinib, accompanied by the PI,
- tofacitinib physician information pack for rheumatologists,

- sponsor-hosted face to face educational meeting(s) for rheumatologists,
- tofacitinib patient information pack (to be provided to rheumatologists for provision to patients initiated on tofacitinib),
- general practitioners and pharmacy information brochure.

Reconciliation of issues outlined in the RMP evaluation report

Table 37 summarises the OPR's first round evaluation of the RMPs, the sponsor's responses to issues raised by the OPR evaluator and the OPR's evaluation of the sponsor's responses.

Table 37: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
The OPR evaluator supports the comments made by the clinical evaluator in that the Safety Specification in the draft RMP is not entirely satisfactory and should be revised, with regard to effects on renal function. The recommendation to the Delegate remains, that the sponsor revises the ongoing safety concerns to include 'Reduction in renal function' as an important potential risk.	The sponsor agrees to include 'Reduction in renal function' into the RMP as an important potential risk, and proposes to update the RMP with this information. To manage the risk, additional language with respect to serum creatinine increase will be included in the proposed Australian PI and educational materials. In addition, the sponsor is committed to conduct routine and enhanced pharmacovigilance activities to continuously monitor and evaluate the risk post approval. The Phase I study of measured GFR in RA patients (A3921152) is ongoing. This study aims to provide additional data to further evaluate the mechanism behind the changes in serum creatinine with tofacitinib relative to placebo in patients with active RA. The CSR will be available for submission at the end of December 2013.	The sponsor's response is satisfactory.
It is recommended that the sponsor provide the draft educational materials (including the medication alert card in the patients information pack) and draft materials for the measurement of effectiveness of the educational program to the TGA for approval prior to the registration of the product in Australia; and measuring the	The sponsor agrees to provide the draft physician educational materials as well as the draft materials for the measurement of effectiveness of the physician educational program to the TGA for approval prior to the registration of the product in Australia. The sponsor also agrees to measure the effectiveness of physician educational materials/initiatives within one year following the launch of the product.	The sponsor's response is satisfactory.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
effectiveness of physician educational materials/initiatives within one year following the launch of the product.		
The RMP evaluator agrees with the third round CER that primary care physicians in Australia are often the first point of contact for patients and they may be less aware of the potential for serious and opportunistic infections and hepatic, renal and cardiovascular risks. The OPR evaluator recommends that these risks are mitigated by the provision of a patient alert card.	The sponsor agrees to provide the patient (medication) alert card (which will be included in the patients information pack) to the TGA for approval prior to the registration of the product in Australia.	The sponsor's response is satisfactory.
The OPR evaluator supports the clinical evaluator's comments that 'risks could also be investigated in further comparative studies with bDMARDs. Pharmacovigilance activities may take many years longer to identify risks than RCTs'. It is therefore recommended that the sponsor conducts post-approval comparative studies with bDMARDs to further characterise the safety profile of tofacitinib. The study protocols should be provided to the TGA for evaluation prior to the commencement of such studies.	The sponsor is currently planning a post-approval comparative study with bDMARDs (A3921133). The primary objective of this study is to evaluate the safety of tofacitinib at two doses (5 mg bd and 10 mg bd) versus a tumour necrosis factor inhibitor; the co-primary endpoints are adjudicated major adverse cardiovascular events and adjudicated malignancies excluding non-melanoma skin cancers during study participation. Secondary safety endpoints will include adjudicated opportunistic infections and other safety events. It is anticipated that approximately 4000 patients will be enrolled; the randomisation scheme will yield a ratio of 1:1:1 (tofacitinib 5 mg bd: tofacitinib 10 mg bd: TNF inhibitor). Recruitment is expected to occur over 3 years and the total duration of the study will be approximately 5 years after the first subject is randomised. The Study Protocol is under review with the US FDA and will be provided to the TGA prior to the commencement of the study.	The sponsor's response is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
Implement AUS-RMP Version 1.2 dated 07 June 2013 [Data lock point 29 September 2011] and any future updates as a condition of registration.	The sponsor is currently revising the Australian RMP (Version 1.2 dated 07 June 2013) with the new data lock point of 19 April 2012 to address all the concerns raised by the OPR evaluator. The sponsor is committed to implement the Australian RMP and any future updates as a condition of registration.	The sponsor's response is satisfactory.
The final RMP evaluator's recommendation to the PI updates is as follows: 'Patients treated with tofacitinib are at increased risk for developing serious infections that may lead to hospitalisation or death, especially in those taking concomitant immunosuppressants'.	The sponsor agrees to update the Australian PI as follows: "Patients treated with Xeljanz are at increased risk for developing serious infections that may lead to hospitalisation or death, especially in those taking concomitant immunosuppressants." This text will be included in the proposed PI as the first paragraph under the sub-section "Precautions, Serious Infections".	The sponsor's response is satisfactory.

Summary

Issues in relation to the RMP

Issues in relation to the RMP for this submission have been adequately addressed by the sponsor.

Advisory committee considerations

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

The following summarises advice provided by the ACSOM:

ACSOM noted the proposed additional pharmacovigilance activities and advised that in many of the studies, tofacitinib was not being used as a third line treatment and therefore the proposed studies will not detect if there are any risks which are specific to tofacitinib when used as a third line agent. Furthermore, ACSOM advised that a washout period is required as tofacitinib is not to be used in combination with a biological disease modifying antirheumatic drug (bDMARD) but the duration of the wash out period has not been well defined in the context of differences in half-life between agents within the class.

OPR evaluator comment:

The OPR evaluator supports the recommendation made by the ACSOM. The sponsor should ensure that the design of the post-approval comparative study enables evidence collection on tofacitinib's use as the third line treatment and allows for sufficient wash out period.

ACSOM noted that there was one case in a clinical trial database which met Hy's Law for DILI and there were two cases which were highly specific for subsequent serious DILI indicating that the risk of DILI could not be ruled out. Therefore, ACSOM advised that the potential for DILI should be more thoroughly addressed in the RMP.

OPR evaluator comment:

The OPR evaluator supports ACSOM's advice. 'Transaminase increases and potential for drug induced liver injury' is listed as an important potential risk in the proposed Aus-RMP. It is recommended that the sponsor undertake to give specific consideration of all reported occurrences of drug induced liver injury in the Periodic Safety Update Reports (PSURs).

Additional advice: there was insufficient guidance for prescribers on the dosing regimen and in particular, information on when to prescribe the 10 mg dose. The committee noted that the PI advised that some patients may benefit from an increase in dose to 10 mg bd based on their clinical response. However, the committee did not consider this was sufficient guidance for prescribers. It was not clear to the committee in what circumstances you would increase the dose. ACSOM advised that dosing should be based on empirical evidence and advised that consideration be given to providing more guidance in the PI.

OPR evaluator comment:

This advice no longer applies to the current submission as the sponsor has withdrawn the application to register the 10 mg tablet strength. However, this information has not been adequately reflected in the current AUS-RMP version 1.2. The sponsor should update the AUS-RMP to delete comments related to 10 mg bd dose under 'Dosage'.

Comments on the safety specification of the RMP

Clinical evaluation report

The Office of Medicines Authorisation (OMA) of the TGA has provided the following comments in the Fourth round CER:

> *'The risk of QTc prolongation is not sufficient to preclude authorisation, but would be sufficient to be included in the RMP as an important potential risk. The risks of infection and malignancy appear to be similar to those for bDMARDs....*
>
> *The sponsor provided new clinical information after the first round and revised the Safety Specification in the draft RMP.*
>
> *The sponsor has agreed to include 'Reduction in renal function' into the RMP as an important potential risk, and proposes to update the RMP with this information.*
>
> *In the opinion of the Evaluator, QTc prolongation should also be included in the RMP as an important potential risk.'*

OPR evaluator comment:

The OPR evaluator supports the recommendation made by the clinical evaluator.

'Serious and other important infection' and 'malignancy including lymphoma' have been included in the current AUS-RMP.

The sponsor has proposed to add text in the PI regarding 'reduction in renal function'[49].

[49] Details of text proposed for the PI are beyond the scope of the AusPAR.

The sponsor should add 'QTc prolongation' into the AUS-RMP as an important potential risk. Other relevant parts of the AUS-RMP including the pharmacovigilance plan and the risk minimisation plan should be updated accordingly.

Recommendation

The following was recommended to the Delegate for the conditions of registration.

RMP

- Implement AUS-RMP Version 1.2 dated 07Jun2013 (Data lock point 29SEP2011) and any future updates as a condition of registration.

Additional condition of registration:

- The sponsor commits to providing the draft educational materials and draft materials for the measurement of effectiveness of the educational program to the TGA for approval prior to the registration of the product in Australia and measuring the effectiveness of physician educational materials/initiatives within one year following the launch of the product.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's Overview, dated 30 December 2013:

Background

Tofacitinib is a small molecule exerting an immunomodulatory effect via a novel mechanism of action. It is a selective inhibitor of the JAK family of kinases, with a greater inhibition of JAK1/JAK3 than JAK2 or TyK2. By inhibiting heterodimeric receptors associated with JAK 1 and JAK 3, tofacitinib blocks signalling for cytokines including IL-1, 2, 4, 7, 9, 15 and 21. The inhibition of JAK1 attenuates signalling by IL-6 and types I and II interferon. In combination, these effects decrease lymphocyte activation, proliferation and migration. At higher exposures, inhibition of JAK2 signalling may lead to inhibition of erythropoietin signalling. Thus, tofacitinib is the first agent to target intracellular pathways involved in the release of cytokines and amplification of the inflammatory response. Thus it has a novel mechanism of action, and its oral formulation makes it the first new oral therapy for many years, and a more convenient option than the bDMARDs which require parenteral administration.

At the time this Overview was prepared, tofacitinib has been approved in the USA (November 2012) as follows:

> *Xeljanz is an inhibitor of Janus kinases (JAKs), indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).*
>
> *Xeljanz should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.*
>
> Dosage: "*The recommended dose of Xeljanz is 5 mg bd*".

The EMA refused market authorisation for tofacitinib after a series of modifications to the proposed indications and a review. The final negative opinion was given on 25 July 2013, for the indication: *Tofacitinib, in combination with Methotrexate (MTX), is indicated for treatment of moderate to severe rheumatoid arthritis in adult patients who have had an inadequate response or are intolerant to previous therapy with at least one biological DMARD. Tofacitinib can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tofacitinib has been shown to improve physical function.*

In Europe, approval for tofacitinib was not recommended by the CHMP on the grounds of insufficiently established safety and efficacy for the proposed population. In the final CHMP assessment report (dated 25 July 2013), the grounds for refusal were "significant and unresolved concerns" about the overall safety profile of tofacitinib, including the risk and type of serious infections and serious adverse effects such as some cancers, gastrointestinal perforations, liver damage, and increased blood lipid levels. The committee was uncertain whether these risks could be managed successfully. The CHMP decided that overall, the data showed that tofacitinib improved disease signs and symptoms and physical function, but that there was insufficient evidence that it consistently reduced disease activity and joint structural damage, especially at the 5 mg dose and in patients in whom at least 2 other DMARDs had been unsuccessful.

The Xeljanz application was still under evaluation in Canada.

Xeljanz 5 mg dose had been granted registration for use in Japan, Argentina, Colombia, Kuwait, United Arab Emirates.

Xeljanz has been approved in Switzerland for the following indications:

> *tofacitinib 5 and 10 mg twice-daily (bd) as monotherapy or in combination with a disease modifying non-biologic antirheumatic agent (DMARD), including methotrexate (MTX), in adult patients with moderate to severe active RA who have had an inadequate response or intolerance to MTX.*

Xeljanz at the 5 mg and 10 mg doses has also been granted registration in Russia.

Summary of the submission history within the TGA

This submission was first lodged in March 2012, and a 'stop-clock' agreed after two rounds of clinical evaluation within the TGA had been completed, after the CHMP recommended that tofacitinib be refused market authorisation in Europe. A mutual 'stop-clock' was agreed to allow the sponsor to submit further studies and the response to the CHMP's concerns. Following this, the clinical evaluators recommended approval of an amended indication as third line not second line (after failure or intolerance of both a tDMARD and bDMARD) and also sought submission of the ECG data for the newly submitted efficacy study. When these ECG data were reviewed, both the Delegate and clinical evaluator had significant concerns about the safety signals raised such that neither could support the registration of tofacitinib without further information and data. It was agreed that the sponsor would not be able to prepare an adequate response to questions and issues raised in the Third round CER and the Delegate's initial Overview and Addendum (see above), and therefore a mutually agreed 'stop-clock' was arranged for a Fourth round of evaluation. The following Overview was written after the Fourth round CER was completed.

Quality

The pharmaceutical chemistry evaluator has no objections to the proposed registration of tofacitinib (Xeljanz) 5 mg with respect to chemistry, quality control and biopharmaceutical aspects.

The proposed products are immediate release, film coated tablets and come in starter pack sizes of 14 (starter pack) and 56 tablets (blisters) and in HDPE 60 and 180 tablets (bottles) with PP child-resistant closures. The stability data provided support a shelf life of 2 years when stored below 30°C in the proposed packaging.

Four biopharmaceutic studies have been evaluated and demonstrated an oral bioavailability of 74%, and demonstrated bioequivalence between the [then] proposed 10 mg commercial formulation[50] and 2 x 5 mg tablets used in the Phase II and Phase III studies. Under fed conditions, the AUC increased by approximately 6% and the Cmax decreased by approximately 32%. The 90% CIs for the ratio of $AUC_{0-\infty}$ were within the range 80.0-125.0% while those of Cmax were outside this interval.

The relative bioavailability of the Phase IIa formulations (2 x 5 mg tablets and 2 x 20 mg tablets) and an oral solution formulation (50 mg oral powder for constitution) were examined. A formal justification for not submitting bioequivalence data for the proposed 5 mg tablet was not provided; however the sponsor provided data addressing the requirements of section 4 of Appendix 15 of the ARGPM that is acceptable from both the pharmaceutical chemistry and clinical perspectives.

The application was considered at the 149th meeting of the PSC of the ACPM on 21 January 2013. The subcommittee endorsed the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic aspects of the submission. The pharmaceutical chemistry evaluator did draw the Delegate's attention to the 180 tablet bottle size. Given this is a drug with significant toxicities and there is a narrow therapeutic window demonstrated in monkeys with repeat dosing studies (3 x AUC was toxic), there is the potential for concern regarding risk of overdose with such a large number of tablets.

The final report released by the CHMP raised quality issues as part of the grounds for refusal of the CHMP committee (CHMP Final Assessment dated 25 July 2013) but the pharmaceutical chemist reviewed these and had no new concerns.

Nonclinical

Overall, the nonclinical evaluator assessed the data as in support of the chronic use of tofacitinib monotherapy for the treatment of RA.

The anti-inflammatory effects of tofacitinib were demonstrated in the mouse CIA model and the rat AIA model, most likely mediated by inhibition of the JAK1/3 pathway, with some limited specificity for the JAK2 pathway.

The metabolism of tofacitinib was extensive, with primary metabolic pathways involving N-demethylation, oxidation of the piperidine ring, oxidation of the pyrrolopyrimidine ring, oxidation of the piperidine ring side chain, and glucuronidation. Multiple CYPs are involved in the metabolism of tofacitinib, mainly CYP3A4 with only a minor contribution from CYP2C19. Tofacitinib itself only weakly inhibited these enzymes and therefore, from animal studies, the potential for tofacitinib to interact significantly with other drugs appeared unlikely at therapeutic plasma concentrations.

The nonclinical evaluation of tofacitinib identified most of the toxicities as being predictable on the basis of its mechanism of action as an immunosuppressive agent

[50] The part of the application to register 10 mg tablets was withdrawn by the sponsor following receipt of the Third round clinical evaluation and Delegate's initial Overview

inhibiting the JAK1/3 pathway. Nonclinical studies revealed the presence of bacterial and viral infections, as well as the development of lymphomas likely due to the immunosuppressive effects of tofacitinib. These risks are recognised and included in the PI, with an estimated risk of lymphoma in humans of 0.61 per 100 patient-years. Major toxic effects were evident in the spleen, thymus and lymph nodes (lymphoid depletion), and bone marrow (lymphoid depletion, hypocellularity and associated anaemia). Effects in a number of other organs, including the liver and gastrointestinal tissues were also observed.

Infections were observed in many of the animals that died during treatment. Infections were present in monkeys receiving ≥ 50 mg/kg/day for 4 weeks (11 fold the human AUC). It is expected that due to the immunosuppressive action of tofacitinib, infections may be a concern in clinical practice.

The reversibility of the tofacitinib induced changes was investigated in a 6 week study in rats, a 4 week study in adult monkeys, and a 39 week study in juvenile monkeys. Decreased WBC, RBC, and lymphocyte counts were partially reversed in rats treated at 100 mg/kg for 6 weeks followed by a 4 week treatment free period. Even after this period, the rats displayed small thymus and lymphoid depletion of the bone marrow.

Tofacitinib displayed a low level of toxicity in acute studies. Pivotal repeat-dose toxicity studies included a 6 month study in rats and a 9 month study in adult monkeys. The high dose level in the pivotal monkey study (10 mg/kg/day; exposure margin 3.0; unbound AUC) produced excessive mortality while the high dose in the rat study did not produce excessive mortality or suppress body weight gain at high exposure margins (> 70 times; unbound AUC). Where deaths occurred in the repeat-dose toxicity studies, this was associated with bacterial infections of the kidney, lung alveolar histiocytosis and interstitial inflammation in rats, and with lymphomas, and bacterial and viral infections in monkeys.

No potential for toxicity to CV, CNS, renal or gastrointestinal systems at therapeutic doses was identified. Toxic effects were partially reversible upon treatment withdrawal, with some persistent haematological and lymphoid suppression as well as ongoing abnormalities in AST and/or ALT. No incidences of gastric perforation were noted.

The observed embryofetal lethality and teratogenicity in two species in animal models (teratogenic in rats and rabbits, and effects on rats on parturition, and peri/postnatal development) led the nonclinical evaluator and Delegate to recommend that the drug be placed in Pregnancy Category D to which the sponsor agreed.

Tofacitinib was shown to be excreted in milk in rats, and it is not known whether tofacitinib is secreted in human milk and therefore, tofacitinib should not be used by women who are breastfeeding (stated in the PI).

The weight of evidence suggests that tofacitinib is neither genotoxic nor carcinogenic.

Clinical

Background

The Guidelines used to evaluate the submission were those adapted from the EMA Guidelines for use in Australia: CPMP/EWP/556/95 rev 1/Final. *Points to consider on clinical investigation of medicinal products other than NSAIDS for treatment of rheumatoid arthritis.*

The four rounds of clinical evaluation included data from 44 studies and 14 summaries or analyses as follows:

- 27 clinical pharmacology studies (20 PK, 7 PD studies (including 2 additional studies for Third round evaluation))
- 2 population PK analyses
- dose-finding studies
- 6 pivotal efficacy/safety studies (one was submitted for Third round evaluation following CHMP negative opinion re efficacy and safety)
- 2 long term follow-on studies
- 2 vaccine studies (submitted in Third round)
- an Integrated Summary of Efficacy, Integrated Summary of Safety (including an updated version submitted for additional evaluation, 10 analyses of combined data)
- the sponsor's response to 22 questions and concerns raised by the Delegate following the Third round evaluation
- a safety meta-analysis, a 2 year study report (efficacy and safety) for one of the 5 pivotal trials submitted at Round 1, a table including of updated long term safety estimates (no supporting data or text)

After evaluating the additional clinical data submitted in the Third round, the concerns raised by the EMA and the sponsor's response to those concerns, the clinical evaluator recommended refusing the then proposed indication (Third round CER), highlighting the following issues:

- the sponsor's proposed indication in Australia was inconsistent with and does not adequately reflect the arguments made by the sponsor in response to the CHMP refusal of marketing approval
- the proposed indication does not sufficiently emphasise that the sponsor proposes tofacitinib to be a third line agent[51]
- that healthcare professionals knowledgeable in the management of RA would be required to recognise and manage the safety risks associated with this treatment
- the following clinical concerns
  - serious infections
  - malignancies
  - dyslipidaemia
  - creatinine rise on tofacitinib
  - liver function abnormalities
  - haematological parameter changes (neutrophils, lymphocytes)

However, the clinical evaluator then recommended approval of the following amended indication:

> *Xeljanz is indicated for the treatment of moderate to severe rheumatoid arthritis in adults who have had an inadequate response or are intolerant to previous therapy with both biological and non-biological DMARDs. Xeljanz can be used alone or in*

[51] The sponsor subsequently clarified to the TGA that it had not changed its position in the Australian application that a second line indication is the most appropriate for Xeljanz, based on the scope of the development program and the demonstration of a favourable benefit:risk in RA patients in second line therapy.

combination with DMARDs, including methotrexate. Therapy with Xeljanz should be initiated and monitored by a specialist rheumatologist.

Proposed dosage: 5 mg bd and 10 mg bd.

The Delegate then prepared an Overview (dated 29th August 2013) that recommended further amendment of the sponsor's proposed and clinical evaluator's recommended indication, based on the following:

As a new class of drug (with limited experience of its long term safety) and some improvement in signs and symptoms but no proof as yet in reducing the progression of structural damage (unlike other DMARDs available), and the lower dose (5 mg) having a lesser effect on inflammatory marker levels (ESR), then it may be reasonable to approve tofacitinib in the third line setting, after failure of both a traditional and bDMARD. Patients with progressive RA, for whom all other treatment avenues have been exhausted, may consider the risk/benefit profile acceptable. However, there remain a number of safety concerns with this drug such as gastrointestinal perforations, potential long term CV effects in addition to those predicted for an immunosuppressive agent.

Accordingly, approval for tofacitinib at 5 mg bd could be considered for the following indication:

Xeljanz/tofacitinib 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. In these patients, Xeljanz can be used in combination with methotrexate, or used as monotherapy.

Following the evaluation of the summary ECG data submitted (which indicated a potential for QT prolongation with tofacitinib) in response to the clinical evaluator's Round 3 questions, the safety concerns raised meant neither the clinical evaluator nor the Delegate were able to recommend consideration for registration at all. Without additional data to clarify the uncertainty raised by the apparently increased rate of QT prolongation in the tofacitinib arms of the latest pivotal study, recommendation of consideration for registration was withdrawn.

A further 'stop-clock' was agreed, and a fourth round evaluation undertaken and this Overview is submitted following all four rounds of clinical evaluation and the sponsor's responses.

In response to the Delegate's concerns particularly about safety at doses greater than 5 mg bd, the sponsor amended the proposed indication to be for the 5 mg dose only but is still pursuing registration in combination or as monotherapy, as a second line treatment. In the Australian context, "second line" is considered treatment after failure or intolerance to a tDMARD as these are commenced first (most commonly MTX, otherwise leflunomide); and third line, the introduction of an agent after failure of or intolerance to both a tDMARD and bDMARD (as per clinical evaluator's report and recommended indication, and EMA report).

Thus, the following Overview examines the efficacy of the 5 mg bd dose and utilises safety data from both dose levels to determine any potential safety signals.

Pharmacology

Pharmacokinetics studies

The oral bioavailability was 74% and food delays the absorption, resulting in a reduction in Cmax by 32% but no change in AUC. The parent drug is the active compound, and appears to be subject predominantly to hepatic metabolism via CYP3A4 and to a lesser

extent by CYP2C19, with approximately 30% renally excreted unchanged, with 44% of that renal excretion occurring by active transport (mechanism yet to be established).

The metabolism of tofacitinib was extensive, with primary metabolic pathways involving N-demethylation, oxidation of the piperidine ring, oxidation of the pyrrolopyrimidine ring, oxidation of the piperidine ring side chain, and glucuronidation.

The PK studies indicated that clearance of tofacitinib is significantly affected when there is moderately impaired hepatic function (increased AUC by 65%, Cmax by 49%), severe renal impairment (where GFR< 30 mL/min, AUC is increased by 123%) and is subject to potentially significant drug interactions. Inhibitions of clearance (renal and hepatic) were seen in those taking concomitant fluconazole (AUC increased by 79%; renal clearance decreased from 7.6 L/h to 5.24 L/h), and lowered tofacitinib levels were observed in those taking rifampicin. Elevated levels of tofacitinib (AUC increased by 103%) were seen with concomitant ketoconazole. CYP2C19 function was assessed and these findings were deemed to be independent of that enzyme's function.

The population studies revealed no significant differences in drug levels by age, weight, gender or ethnicity. There was, however, an increased AUC and Cmax for Asian women with RA. The PK study in patients with RA had a representative age range but excluded anyone with severe renal impairment, and moderate to severely impaired hepatic function.

Pharmacodynamic studies

Natural killer cells showed a dose-dependent decrease and B lymphocytes a dose dependent increase across the studies. It was estimated that NK cells would reach a nadir at 8-10 weeks. There was no clear pattern of response among CD3+, CD4+ or CD8+ cell counts.

In the secondary PD studies, tofacitinib increased total cholesterol in patients with RA but the total cholesterol was reduced significantly in those randomised to receive atorvastatin. A secondary study was presented in response to concerns about the effect of tofacitinib on cholesterol levels, and examined the effect on the kinetics of cholesterol flux through the HDL/reverse cholesterol transport pathway in subjects with active RA. The findings suggest that the observed elevation 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.

No effect on renal function nor QTc was observed in healthy volunteers.

The second PD study submitted for the Third round of evaluation examined the production of synovial and serum cytokines and effects in those receiving 10 mg bd tofacitinib versus placebo. After 28 days, there were decreases in NK cell counts in the tofacitinib group which recovered by day 35, and memory B cells which recovered within a day of discontinuing therapy. Other changes were a decrease in serum CD19+ and interferon-stimulated ubiquitin-like protein (ISG)15.

Despite there being no statistically significant differences in the drug levels between Asian and non-Asian populations demonstrated above, the EMA clinical evaluator(s) noted that the percentage of responders is higher for studies 1039/1040, both of which were conducted exclusively in the Japanese population. This may reflect the increased tofacitinib drug levels observed and noted above. Side effects like herpes, opportunistic infections and creatinine increases were also more common in Asians and this again raised the possibility of an exaggerated PD effect. Further studies would be required to clarify this. The sponsor agreed to the Delegate's request to include a warning under *Special Populations* in the PI.

Efficacy

Five dose finding Phase II studies for tofacitinib were conducted, as monotherapy (2) or in combination with MTX (2) or adalimumab (1) (see Table 4 above). As monotherapy, daily doses of 2 to 60 mg daily (in divided doses) were compared with placebo with a plateau of effect observed (for ACR20) at the 15 mg bd dose. In combination with MTX, bd doses ranging from 1-15 mg versus placebo were assessed, with a range of endpoint effects observed from 5-20 mg bd with ACR20 peaking at 10 mg bd. In combination with adalimumab, doses from 1-15 mg bd were assessed against placebo. The ACR20 peaked at 10 mg bd dose. A comparison of the effect of tofacitinib dose on Japanese versus Caucasian subjects all receiving MTX demonstrated no significant difference in effect between the two populations.

The doses of 5 and 10 mg were used for subsequent Phase III studies. In response to the Delegate's concerns about the risk-benefit profile of the 10 mg bd dose (Delegate's initial Overview 29 August, 2013, see above), the sponsor is no longer seeking approval for the 10 mg bd dose, therefore the 5 mg bd dose will be assessed for safety and efficacy.

Pivotal studies

The pivotal analysis comprised efficacy data from six Phase III trials (A3921032, A3921044, A3921064, A3921045, A3921046, A3921069). The first five were randomised, double blind, paired placebo controlled, parallel-group efficacy and safety studies, and all examined the effect of either 5 mg bd or 10 mg bd against paired placebo control. The comparator arm was specified for each trial but was either MTX or a tDMARD plus placebo, with the exception of A3921045 where it was placebo alone. The first two trials (1032, 1044) compared tofacitinib plus MTX with MTX in paired placebo groups, the third trial (1064) incorporated an additional comparator arm of MTX plus adalimumab. Trial 1045 examined tofacitinib as monotherapy in those who had progressed on at least one DMARD (traditional or biological) and the final study (1046) examined tofacitinib in combination with at least one tDMARD versus tDMARD with paired placebo.

In the paired placebo arms in the trials of 6 months' duration, crossing to tofacitinib occurred after 3 months; for those trials of 12-24 months' duration, crossing to tofacitinib was mandated at 6 months but could occur at 3 months where there was treatment failure. The sixth trial (submitted for evaluation after CHMP refusal for marketing authorisation) was a 2 year randomised, controlled trial comparing monotherapy with tofacitinib 5 mg bd or 10 mg bd with MTX alone.

Details of key inclusion and exclusion criteria, patient populations, primary and secondary efficacy endpoints, and safety outcome measures are as described above under *Delegate's initial Overview: Clinical aspects Efficacy*.

Pivotal studies in combination with methotrexate (A3921032, A3921044, A3921064)

Study A3921032 compared 6 months and A3921044 (a 2 year study) compared 12 months duration of tofacitinib added in to MTX, with paired placebo control in subjects with RA already on an established dose of MTX. For A3921032, the control group had placebo for 3 months before advancing to tofacitinib, and for Study A3921044, the placebo control was for 6 months, but subjects could advance at 3 months if there was treatment failure. Study A3921064 had the same design as A3921044 but with the inclusion of an additional arm of adalimumab 40 mg every 2 weeks. All trials required ongoing treatment with a stable dose of MTX (minimum 4 months' duration, stable dose of 7.5-25 mg weekly in 6 weeks prior to first study dose; MTX doses below 15 mg were allowed where intolerance, toxicity or local indication prevented higher MTX dose). All included a wide age range 20-84 years (A3921032), 18-82 years (A3921044) and 18-83 years (A3921064).

Study A3921032 was a 6 month study, with 399 patients with moderate to severe RA randomised into 4 groups (2:2:1:1) to receive either bd 5 mg or 10 mg tofacitinib plus MTX paired with placebo control groups on MTX switched to bd 5 mg or 10 mg tofacitinib after 3 months. The inclusion criteria were that participants had tried at least one TNF inhibiting biologic agent (discontinued because inadequately effective and/or not tolerated) and be on a stable dose of MTX for 4 months prior. An additional 11.5% (identified as 16% in EMA report) on tofacitinib 5 mg and 10% of the MTX control arm patients had taken another bDMARD other than TNF inhibitors; 30.8% had previously taken other tDMARDs (reported as 39.8% in EMA report) in the tofacitinib arms compared with 25% in the MTX/placebo arm. Furthermore, from the Final CHMP assessment report, it is stated that 64.4% had had a single TNF inhibitor, 26% had received two TNF inhibitors, and 8% had received 3 or more prior TNF inhibitors in the whole study population.

After 3 months, adding in tofacitinib 5 mg resulted in a significant improvement in ACR20 in 17% of patients, a change in ESR in small number of patients absolutely (8/119 achieved ESR < 2.6 compared with 2/120 in placebo arm), and an improvement in HAQ-DI of 0.25 compared with placebo ($p = 0.0496$).

Secondary efficacy outcomes were designed to measure the response in the ACR20, HAQ-DI, DAS28-4 in the active treatment groups compared with placebo at 6 months. However, by 6 months, all "placebo" patients had crossed over to active treatment with tofacitinib for 3 months, thus there is no longer a control group for comparison. Quality of life measurement using SF-36 demonstrated an improvement at 3 months not seen at 6 months, and the WLQ was inconclusive.

Comments: The absolute benefits of adding 5 mg tofacitinib are very limited with fewer than 1 in 5 achieving an improvement in signs and symptoms, as judged by the ACR20 response (the least stringent criterion in the ACR response scale) and 1 in 20 achieving an DAS28-4 (ESR) < 2.6 at 3 months better than the MTX alone control arm; the change in HAQ-DI is minor and just reaches statistical significance. While it appears that efficacy has been demonstrated, it is relatively weak, and the significance of these findings are undermined by the trial design.

- It is very difficult to be clear about how many prior lines of therapy these patients had received from the data submitted: all were required to be on a stable dose of MTX and had had a prior TNF inhibitor, thus two lines as a minimum; however, for some, tofacitinib is being examined as, at the minimum, a third, fourth or fifth line of therapy: this is very far removed from the population for which the sponsor is seeking registration, and the findings cannot be extrapolated.
- Beyond the 3 month point where the placebo group commenced active treatment, it ceases to be a randomised controlled trial and no comparative data are available. Any statistics can only be descriptive after this time point.
- The choice of single agent MTX as a comparator, especially for those who have previously required one or more TNF inhibitors, plus other tDMARDs and bDMARDs and thereby defined themselves as poor responders, would appear to be likely to fail single agent MTX therapy. This would not be the standard of care for such patients.
- The minimum permitted dose of MTX of 7.5 mg is very low (and beneath the 10 mg minimum allowed in the pivotal study A3921069 comparing tofacitinib versus MTX alone), and may well have resulted in a poorer response rate in the placebo/MTX arm.

Thus, this is a very heterogeneous population with respect to nature and number of prior treatments, and is not consistent with the sponsor's proposed second line indication. Efficacy in terms of signs and symptom improvement has been demonstrated in a low percentage, the HAQ-DI change is not large and DAS28-4 (ESR) response rate is not

significant and does not support there being any modification of the underlying inflammatory process. Additionally, there are trial design issues which undermine whether these efficacy outcomes have been satisfactorily established.

Study A3921044 was a 24 month study comparing tofacitinib plus MTX with 3-6 months of paired placebo/MTX; advancement to treatment with tofacitinib/MTX occurred for those not a responder (subjects who failed to achieve a minimum improvement of at least 20% reduction in swollen and tender joint counts) from 3 months, otherwise all placebo/MTX groups commenced tofacitinib at 6 months. Additional inclusion criteria were presence of active RA with joint erosions or positive Rheumatoid Factor (RF+) or antibodies to cyclic citrullinated peptide (anti-CCP) or evidence of ≥3 distinct joint erosions on PA hand or wrist radiographs. Two year data were submitted for Study 1044 for the Round 4 evaluation.

800 patients, aged 18-82 years, were randomised 4:4:1:1. 797 received treatment with completion rates consistent across the different groups. In the tofacitinib 5 mg/MTX group, 60% had had prior treatment with at least one tDMARD (193/321 patients had received a total of 331 tDMARD therapies), and 5.3% had received a prior bDMARD (17/321 patients had received a total of 18 bDMARD therapies). In the placebo arm, 67.5% (108/160 patients had received a total of 199 therapies) had received at least one tDMARD and 3% (5/160 patients had received bDMARD therapies) had had a prior bDMARD.

Adding tofacitinib 5 mg to MTX resulted in a significant improvement in ACR20, with 51% responding compared with 25% in the MTX/control group after 6 months. The endpoint of mTSS did not show any significant slowing of joint destruction progression at 6 months in those receiving 5 mg tofacitinib bd. Therefore, statistical significance for the primary endpoints, DAS28-4(ESR) and HAQ-DI could not be claimed for the tofacitinib dose due to the pre-specified step down procedure which required the preceding primary efficacy variable (mTSS) to have been statistically significant. 5% more patients achieved a DAS28-4 (ESR) < 2.6 with adding in 5 mg tofacitinib dose (percentages: 7% for tofacitinib 5 mg/MTX compared with 1.5% in placebo/MTX), and there was a -0.25 change in the HAQ-DI at month 3.

The 2 year results were presented for evaluation in Round 4. It is not possible to determine the efficacy of this dose on any of the parameters at 24 months as there is no meaningful control group as all have been on active treatment with tofacitinib/MTX for 18-21 months.

Other secondary efficacy outcomes were to assess the response in the ACR20, HAQ-DI, DAS28-4, mTSS in the active treatment groups compared with placebo at 12 months, but both the imputation of those dropping out as non-responders, together with the effects of crossing to the active treatment at 6 months, means there is no randomised, control group for comparison. For the remainder of the secondary efficacy outcomes measured within 6 months, there were a range of responses: fatigue measurements were reported to have improved in the active treatment arms, and at 3 and 6 months the SF-36 responses indicated an improvement. The WLQ and MOSS-SS (sleep disturbance scale) responses indicated no effect of active treatment at month 6.

Comments: Tofacitinib in combination with MTX is reported to improve the ACR20 response in 26% more patients, but demonstrated no change on the structural progression nor the inflammatory markers, suggesting there is no modification of the underlying inflammatory processes, which are correlated with an increased risk of debilitating loss of function long term.

Several issues in trial design and protocol violations give rise to concern:

- For 40% of the tofacitinib arm, MTX was the first treatment. The sponsor (in the response to the Delegate's initial Overview, above) described a lower rate of progression than expected. Given the shortest disease duration at commencement was only 2.4 months (yet all were required to be on a stable dose of MTX for 4 months prior), many may have been responding to MTX when tofacitinib was introduced, especially the previously untreated. Thus, there is some doubt that this is the population as defined by the indication sought: those *"who have had an inadequate response or are intolerant to previous DMARD therapy"* that is, they are not genuinely second line.
- 60% and 67% in the tofacitinib and control arm respectively, had had a prior tDMARD other than MTX (second line); some had more than one other tDMARD, and a small number had had a bDMARD. This indicates a very heterogeneous trial population.
- Those who dropped out of the study were imputed as non-responders, regardless of the reason, which potentially biases the results and it also both depletes and redefines the placebo arm. By the 6 month mark, the numbers in the control arm had decreased.
- There was no demonstrated effect on structural progression at any time-point with the 5 mg dose. The EMA Guidelines adopted in Australia by the TGA recommend radiological demonstration of a lack of progression using full randomisation (that is, control arm for duration of study, preferably 24 months), with imaging done "not less than one year apart ideally for two years using full randomisation". The measurements were done here at 6 months (no effect observed, as would be expected as this is considered too soon to detect a change), and at the 12 month and 24 month time points when all patients had received tofacitinib for at least 6 and 18 months respectively, so there is no longer a comparator against which to demonstrate effect. The sponsor, in response to the clinical evaluator's comments to this effect, maintains that the 24 month results demonstrate an ongoing effect of tofacitinib on decreasing structural progression; however, without a control population, it is not possible attribute this to tofacitinib, especially in a disease that waxes and wanes.
- Primary efficacy measurements were missing for up to 15% of subjects (for example, DAS28-4 (ESR)) in the tofacitinib group. Given the absolute reported benefit of 5% was so marginal, this could change the result if all the data were recorded in that group. Statistical significance could not be claimed for the DAS28-4 (ESR) as the mTSS endpoint was not significant as required due to the pre-specified step down procedure for ranking endpoint importance.
- The early escape design then mandated crossing to the tofacitinib arm at 3 and 6 months, respectively, were utilised as it would be unethical to keep patients on the MTX/placebo treatment if their disease was progressing. However, it removes the randomisation (from 3 months) and as there is no longer a control arm, it essentially becomes an extension trial beyond 6 months. At 6 months, the addition of 5 mg bd tofacitinib to MTX appears to improve the clinical signs and symptoms in 1 in 4 patients, but the extent of that improvement over and above the MTX/placebo, and therefore its statistical significance, is uncertain due to the classification of non-responders and diminished MTX/placebo numbers by that time.
- The effect of tofacitinib on the HAQ-DI and ESR was modest at best and not statistically significant.
- Data for the primary endpoints were missing from the 5 mg treatment group as follows: DAS28-4 (ESR) (15% = 44 patients), mTSS (10%), HAQ-DI (5%).
- There is an extremely wide range of duration of disease (from newly diagnosed 0.2 years up to 49 years).

Thus there appeared to be an improvement in the ACR20, but no change in the underlying inflammatory disease process or prevention of structural damage was demonstrated. Furthermore, it is not clear what proportion of this population could be regarded as second line as defined by the sponsor's proposed indication; there were also some third line patients included. This is not conclusively supportive of the second line indication, and only improved the signs and symptoms, nor the broader treatment benefits implied in the wording of the proposed indication.

Study A3921064 was a one year study in patients already on a stable dose of MTX designed to compare the efficacy of adding in tofacitinib 5 mg or 10 mg bd compared with paired placebo; a further arm received adalimumab in addition to MTX, however, it was not designed as a superiority nor non-inferiority study so tofacitinib was not compared with adalimumab. Exclusion criteria were: prior failure of a TNFα inhibitor, any prior treatment with adalimumab, and to permit safe randomisation to the adalimumab arm, those with Class III or IV heart failure (New York Heart Association) or any other contraindication to adalimumab were excluded. Primary efficacy endpoints were the same as for Study 1044, but without the mTSS scores.

717 subjects, with moderate to severe arthritis for between 0.2-49 years, on stable doses of MTX were randomised 4:4:4:1:1 to receive bd doses of 5 mg or 10 mg tofacitinib, 40 mg adalimumab SC every fortnight or paired placebo (with tofacitinib introduced at 3 months if no response (subject failed to achieve a minimum improvement of at least 20% reduction in swollen and tender joint counts), or for all at 6 months). Prior DMARD use was recorded in 53.4% in the tofacitinib 5 mg arm, 54.7% in the placebo and 55.9% in the adalimumab arm and previous bDMARD use had occurred in 1% of the tofacitinib group, 5.4% of the placebo group and 1.5% in the adalimumab group.

Primary efficacy endpoints were the ACR20, DAS-28-4 < 2.6 at 6 months and HAQ-DI at 3 months.

At 6 months, tofacitinib/MTX, and adalimumab/MTX resulted in an ACR20 in 51.5% and 47.2% patients respectively compared with 28% for the placebo arm. Although reported to be statistically significant, the absolute benefit of tofacitinib was low for DAS28-4 (ESR) score reduction < 2.6: 5.2% (6.2% compared with 1% in placebo, $p < 0.001$) and 5.7% in the adalimumab/MTX arm. Data was missing for the DAS28-4 (ESR) in 10% of the 5 mg group, 10% of the adalimumab group and 14% of the placebo group. The HAQ-DI change (-0.31) in the tofacitinib group at 3 months was significantly better compared with the placebo ($p < 0.001$).

There was no apparent difference in HAQ-DI and ACR20 scores between the 5 mg tofacitinib and adalimumab treatment groups.

Other secondary efficacy outcomes were:

- ACR20, HAQ-DI, DAS28-4 at months 3 and 6
- ACR 50 and 70 at 3 months (but no control group after 6 months): only the ACR70 was different in favour of the tofacitinib group (19.9% versus 9%, $p = 0.0019$). This was not a study designed to compare these two therapies
- reduction in DAS28-3 (CRP), an improvement in fatigue levels and EQ-5D from 3 months to the 6 Month point

SF-36 at Month 6 was improved for tofacitinib compared with placebo but not adalimumab to the same extent. Significant improvement in sleep compared with placebo was noted for the tofacitinib groups, with some improvement noted for adalimumab at 6 Months. The WLQ indicated no change with active treatment.

Comments:

- The issues identified with Studies 1032 and 1044 pertain to this trial also (see above for discussion of issues): those who dropped out of the study being imputed as non-responders, regardless of the reason, which has potential to bias the results, and the early escape design from 3 months, followed by mandated crossing to the active arm meaning there was no randomised placebo group for comparison beyond 3 months. Data collected at the 6 month point will be in a depleted control group. Thus, comparative efficacy outcomes beyond the 6 month point have not been considered by the Delegate, and those beyond the 3 month point are interpreted with caution. This particularly affects findings where the differences are small, for example, the DAS28-4 (ESR). The ongoing efficacy data beyond 6 months may provide some maintenance information but a treatment effect is difficult to determine in a disease that waxes and wanes as part of its natural course.
- Data were missing for the DAS28-4 (ESR) measurements which, given the very small difference could have a significant impact on the outcome of this. Data from 22 subjects were missing in the tofacitinib arm, and 14 in the placebo/DMARD arm. With only 11 more patients responding in the tofacitinib arm, these missing data could potentially change at least the statistical significance, if not the result.
- Some patients had very longstanding disease and as such, would be likely to have tried more lines of therapy (including a bDMARD) and be potentially more difficult to treat effectively. Equally, some patients had just been diagnosed for 2 or 3 months and it could have been too early to judge and possibly unnecessary to introduce a potent DMARD in combination with MTX. The highly varied population with respect to disease duration and lines of prior therapy make it difficult to interpret who might benefit from this strategy of combination therapy. As with Study A3921044, there may be some uncertainty as to whether the population are those who have failed or been intolerant of a prior DMARD therapy.
- This trial uses a comparator arm of adalimumab, a proven bDMARD, which would be the next step for patients with disease progressing after a tDMARD; however, it was not designed to compare tofacitinib with adalimumab (that is, not a superiority nor inferiority study) and only general observations about the relative responses can be made.

There is a statistically significant improvement in the signs and symptoms and quality of life for those receiving tofacitinib in addition to MTX compared with MTX alone. These results were generally similar to those obtained with adalimumab, but this was not designed to show this. There was a statistically significant but very low absolute improvement in the DAS28-4(ESR) response, but the missing data and imputation of those discontinuing as non-responders cast doubt on the validity and statistical significance of this finding. Once again, there is a very variable population, with some uncertainty as to which patients were benefiting.

Pivotal study as monotherapy

Study 1045 was a 6 month study of 3 months of tofacitinib as monotherapy compared with paired placebo groups in those with RA who had an inadequate response or were intolerant to treatment with at least one prior DMARD (traditional or biological). The exclusion criteria were similar to the above trials, with no requirement for previous or concomitant treatment with MTX, and all must have had an adequate washout period of any discontinued therapy prior to commencement. Concomitant use of stable doses of antimalarials was permitted, as was maintenance on a stable oral glucocorticoid dose ≤ 10 mg/day.

Primary and secondary efficacy endpoints were as for Study A3921032. The sample size was not stated in the study report but the determinants for each endpoint was the same as for Study A3921032, and hypothesis tests were performed in the same manner.

611 subjects were randomised 4:4:1:1 to receive 5 mg or 10 mg tofacitinib bd, with paired placebos switching to 5 mg or 10 mg after 3 months. 610 commenced and 555 completed the study treatment. Prior to enrolment, 84.9% had taken MTX, 66.4% had taken a tDMARD other than MTX, and 6.7% had used a bDMARD. Concomitant antimalarials were taken by 18.4% in the 5 mg group, 13.1% in the placebo/5 mg group and 11.5% in the placebo/10 mg group. The number on glucocorticoid therapy is uncertain.

Of the primary efficacy endpoints at 3 months, 59.8% of patients on tofacitinib achieved an ACR20 response compared with 26.7% in the placebo arm, and HAQ-DI was significantly improved by active treatment compared with placebo (LS mean difference of -0.31), while DAS28-4 (ESR) < 2.6 did not change (5.6 for the tofacitinib group compared with 4.4% for the placebo). Other secondary efficacy outcomes were the absolute maintenance of the response in the ACR20 and HAQ-DI at 6 months, however as crossover occurred at 3 months to tofacitinib in the placebo group, there is no control group for comparison. Other secondary outcomes at 3 months included the quality of life measure SF-36 at month 3, which showed some improvement in the tofacitinib arm. There was some improvement in DAS28-3 (CRP), EQ-D5, and some elements of the fatigue scales in the active treatment groups compared with placebo at 3 months. No difference was seen in the WLQ responses at month 3.

Study outcomes

At 3 months, one third of the 5 mg tofacitinib group experienced a 20% relative improvement in clinical signs and symptoms (ACR20) compared with the control group, and reported an improvement in quality of life but there was no influence of tofacitinib on inflammatory markers (at 3 months). This raises the concern that tofacitinib monotherapy in this second and third line population exerts no effect on the underlying inflammatory disease process. Thus it is unlikely to influence the long term debilitating aspects of RA, such as progressive joint destruction, in the pre-treated population, which is the group in which the indication has been proposed.

Study design

There were the problems with the study design and crossing to the treatment arm, as reported previously, so no consideration can been given to comparative efficacy data presented after the 3 month point in the 6 month trials; and 6 month mark for the 12 month data from the 12-24 month trials.

- The trial was not monotherapy versus no treatment, as concomitant antimalarials which are also DMARDs were permitted, and the arms were not balanced: 6% more patients in the tofacitinib group received concomitant antimalarials compared with the control group, which would favour the treatment arm.
- This trial includes a mixed population in terms of how many prior lines of treatment patients had received; if two thirds had taken a tDMARD other than MTX, and 84.9% had had prior MTX, it would be the third treatment or beyond for the majority before even considering usage of bDMARDs. In the response to this Overview, the sponsor was requested to provide a numerical breakdown of the subjects by number of lines of prior therapies (see *Questions for sponsor*, below).
- In a pre-treated population with active, moderate to severe disease who have not yet exhausted all other proven options for treatment, 'no active treatment' is not the current appropriate standard of care for establishing a second line indication. Such patients in Australia would normally be commenced on MTX, progressing on to MTX/leflunomide and to MTX/bDMARD whereas the sponsor is seeking registration of

tofacitinib alone in this setting. A no-treatment arm would only be appropriate where patients had exhausted or were intolerant of all prior therapeutic options, that is, testing tofacitinib as a 'last resort'. This is not consistent with the second line indication sought by the sponsor.

Conclusion

Taking into account the issues raised above regarding trial design:

- there is some efficacy in improving the signs and symptoms of RA with the addition of tofacitinib but the exact population benefiting is not clear: this is not a population receiving monotherapy (some of the response may possibly be attributable to the antimalarials)
- there is no clearly established effect on the underlying inflammatory process
- this study was not designed to, nor makes any claims regarding structural preservation with tofacitinib monotherapy

Pivotal study as concurrent treatment with DMARDs

Study A3921046

This was a 12 month study of tofacitinib in combination with a tDMARD (although prior use of bDMARDs was permitted) compared with paired placebo groups (who likewise were on a background DMARD) in those with moderate to severe RA. Additional criteria included having at least 4 tender, painful joints on motion (out of 68 joints assessed) and at least 4 swollen joints (out of 66 assessed), and the subject must be on a tDMARD and remain on that for the duration of the study. Traditional DMARDs were permitted, but others could be included after discussion with the sponsor. The DMARDs used included MTX, sulfasalazine, leflunomide, hydroxychloroquine sulphate, injectable gold and penicillamine. Efficacy outcomes were the same as Trial A3921032 except that primary efficacy outcomes were measured at month 6.

795 subjects with a variable duration of moderate to severe RA (the lowest mean duration was for the tofacitinib 5 mg arm: 8.1 years (0.2-49 years)) were randomised 4:4:1:1 to receive bd doses of tofacitinib, 5 mg or 10 mg, or paired placebo groups who switched to bd doses of tofacitinib 5 mg or 10 mg at 3 months if a response was not achieved (subject failed to achieve a minimum improvement of at least 20% reduction in swollen and tender joint counts), and all remaining in the placebo groups switching at 6 months. The age range was 18-86 years, the mean age 52, and 14% were over 65 years of age. All had taken DMARDs prior to screening, the most common being used MTX (84%) followed by leflunomide, and TNFα inhibitors had been taken prior to screening by 7.3% of subjects in the 5 mg group and 6.3% in the placebo group. Other bDMARDs had been used in 2.2% and 3.8% for tofacitinib 5 mg and the placebo arms, respectively. Within the trial, 33% were taking combination therapies, and 66% single tDMARDs.

For primary efficacy outcomes, the active treatment resulted in a significantly improved ACR20 in 21% (CI 12.4% -30.7%), and a small improvement in HAQ-DI compared with placebo at month 3 (-0.26). A DAS28-4 (ESR) < 2.6 was reported to be achieved in 6.4% more patients in the tofacitinib arm but significant numbers were missing for this (see second comment below).

The trial design issues already identified pertain to this trial, including:

- The early escape and mandated crossing to active therapy, with the consequent loss of randomisation and resulting in a reduced and redefined control population. Data collected beyond 6 months cannot be used for comparative purposes. The imputation of those discontinuing as non-responders, regardless of reason, means all data beyond

3 months, must be interpreted with caution as it is no longer a randomised, controlled trial.

- 66% were on a single DMARD plus tofacitinib whereas one third was taking more than one DMARD plus tofacitinib during the trial. The distribution between the arms is not clear and therefore it is not clear whether the combination therapy might be responsible for the differences observed.
- There was a small absolute benefit reported in reducing inflammation after 6 months in the tofacitinib arm. However, the data for 16.5% of patients in that arm and 7% in the placebo arm were missing. The impact of the missing data (52 patients in the treatment arm) is potentially significant; thus, it is not clearly established that tofacitinib reduces inflammation when added to a tDMARD.
- Many of the secondary efficacy outcomes were reported after 12 months of treatment; however, by this time all patients were receiving tofacitinib so there is no control arm to permit comparison. Those improved within the timeframe where there was a control included: quality of life ratings such as the EQ-5D, which improved at 3 and 6 months, and sleep which improved at 3 months but was not maintained at 6 months. There was no significant difference as measured by WLQ. This study was affected by the low numbers in the placebo groups.

Conclusion

Taking into account the issues raised above regarding trial design, there appears to be:

- some improvement in the signs and symptoms of RA with the addition of tofacitinib to background DMARD therapy, that is, combination therapy (although one third of patients were taking >1 tDMARD, the rest were taking single tDMARD).
- no clearly established effect on the underlying inflammatory process
- a different target population from that in the proposed indication (10% had used a bDMARD so this is third line treatment for that group; clarification is to be sought from the sponsor, see *Questions for sponsor* below), and therefore efficacy in a different population from that sought for registration as second line.

Pivotal study as comparator with MTX

Study A3921069 was a multicentre, 2 year, randomised, double blind, parallel group comparator controlled trial with three arms: tofacitinib 5 mg or 10 mg bd in comparison with MTX alone in subjects with moderate to severe RA and no prior use of MTX. Patients could have received prior traditional or bDMARDs but must be MTX-naïve, that is, tofacitinib is either first, second or later line of therapy. The study was submitted for evaluation in response to concerns expressed by the CHMP about safety and efficacy, and had not been evaluated by the FDA prior to registration in the US. It follows the EMA Guidelines for a parallel design, but this time there is no early escape or crossing to the active arm.

Additional inclusion criteria were:

- 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 be 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 (previously ≥ 4).

- No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB)

Additional exclusion criteria were:

- 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
- GFR < 60 mL/min (previously < 40 mL/min for other trials)
- 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

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 primary efficacy outcome measures were structure preservation as measured by mTSS at Month 6, and signs and symptoms as measured by ACR70 at Month 6.

The secondary efficacy outcome measures aimed to identify joint structure preservation, signs and symptomatic control, physical function and patient-reported outcomes. Structure preservation was determined by assessing actual and mTSS change from baseline at months 12 and 24, actual and any change in two individual components of mTSS: erosion and joint space narrowing (JSN) scores at Months 6, 12, and 24, non-progression of mTSS (mTSS change ≤ 0.5) and rate of "no new erosions" (erosion score ≤ 0.5). Differing levels of DAS28-3 (CRP) and DAS-28-4 were used, and durability of ACR20/50/70 responses was used to determine biochemical and clinical responses respectively. Tools for measuring physical function and quality of life were those used in the other trials.

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

958 patients were randomised 2:2:1 and 952 received either bd tofacitinib doses of 5 mg or 10 mg or MTX 10 mg/week titrated up to 20 mg/week over 8 weeks according to tolerance. All previously used DMARDs were discontinued with a treatment-specified wash out period. The age characteristics were very similar across all three arms, with a range of 18-83 years, mean ages of 48-50, and 10-11% of subjects were over the age of 65. The median disease duration was 0.7 years for both tofacitinib 5 mg (range 0-44 years) and MTX (0-30 years) groups but both groups included patients with a long duration of disease. Two thirds of the patients in each arm had had RA for < 2 years and for the majority, this was the initial treatment. 37% of patients in the tofacitinib arm and 41% in the MTX arm had received prior tDMARD therapy.

For the two primary efficacy endpoints (measured at 6 months), 5 mg bd tofacitinib resulted in 13% more patients achieving an ACR70 (95% CI for difference 7.05-19.97, $p < 0.0001$) with the absolute numbers responding on tofacitinib being 25% compared with 12% in the control arm. The reductions in mTSS scores relative to MTX at 6 months were significantly lower in favour of tofacitinib 5 mg at -0.66 (95% CI -1.03 to -0.28, $p < 0.0006$).

The secondary endpoints generally supported a greater magnitude and duration of effect of tofacitinib compared with MTX. Specifically, statistically significant increases in ACR20, 50 and 70 were seen from month 2-12 and the number with no progression as determined by mTSS at 12 months was significantly greater for tofacitinib 5 mg (81.16%) compared with MTX (64.71%), $p < 0.0001$. Data for evaluation of any other structural assessments beyond 12 months were not available in time for evaluation in the Fourth round clinical evaluation and the sponsor is requested to provide a synopsis of the study results for both efficacy and safety in response to this Overview. A non-significant improvement in inflammatory markers was seen with 5 mg tofacitinib compared with MTX at 12 months.

Comments:

- The sponsor identifies this as a first line trial and as this is not the population for which the indication is being sought, the outcomes are not relevant in this submission. The trend to a smaller effect of tofacitinib in those with prior DMARD treatment(s) is consistent with the difficulty of treating diseases that have previously failed other therapies, and demonstrates why the findings cannot be generalised to the pre-treated population in which the indication is being sought.
- The mTSS is being measured at an earlier time point than considered acceptable for demonstrating structural benefits; thus, the 6 month outcome is not appropriate for determining and demonstrating efficacy (see EMA Guideline CHMP/EWP/556/95 rev 1 *Points to Consider on Clinical Investigation of Medicinal Products Other than NSAIDs for Treatment of Rheumatoid Arthritis.*).
- Those who discontinued for any reason were treated as non-responders, which may favour the tofacitinib arm, particularly given the long duration of the study and fixed doses of MTX required by the study design beyond 3 months.
- The numbers receiving either more than one prior treatment, or who used bDMARD(s) were not clear. The reported rates of prior DMARD usage were 37% and 41% in the tofacitinib and MTX arms, respectively, but the prior use of individual tDMARDs tallied 165 in the tofacitinib arm (165/373 = 44%) and 95 (95/186 = 51%) in the MTX arm. This may represent uses of multiple DMARDs by individual patients, possibly sequentially (affecting numbers of prior lines of therapy), and the sponsor will be requested to clarify this (see *Questions for sponsor* below).
- Additional issues about MTX comparator arm:
  - The MTX dose levels in 20% of subjects were 10 or 15 mg/week which may be suboptimal, especially in a pre-treated population
  - 15% MTX doses are not accounted for
  - MTX doses were increased in 5 mg increments every 4 weeks, with a 5 mg reduction permitted once (as long as the dose was ≥ 10 mg/week), then fixed from 3 months; thus, no titration was permitted beyond this point
  - Due to blinding MTX had to be an oral formulation, not parenteral, limiting optimisation strategies for managing MTX intolerance

Any under-treatment with an associated increased risk of progression in the MTX arm would favour and may lead to overestimation of the benefit of tofacitinib.

- A manuscript prepared by the sponsor for submission for publication (but not accepted for publication so not peer-reviewed) was submitted at Round 4 (this was

not formally evaluated[52]). Essentially, this study was in a population not pertinent to the submission. The methods and results are not reported in sufficient detail for the report to be evaluable in support of efficacy or safety. It is not stated how missing data were imputed and how many subjects in each treatment group were included in the analysis of efficacy at each time point. The safety data are incomplete and do not include any discussion of ECGs, one of the major issues identified in the current application (See *Safety* below).

The manuscript and an 'expert opinion" (included in the Round 4 submission) claim the findings in this study substantiate 2 year results from Study A3921044 (tofacitinib as a second line therapy)." Neither the clinical evaluator nor the Delegate considers that there was any demonstrated significant efficacy of 5 mg tofacitinib in Study A3921044 at 6 months, and definitely not at 24 months. Furthermore, the Delegate does not believe Study A3921044 could be defined as a second line trial.

Other efficacy studies

Long term extension studies A3921024, A3921041

The primary endpoints of these two studies were the safety and tolerability of longer term use of tofacitinib, and ongoing efficacy was a secondary outcome.

Study A3921024 is an ongoing open label, long term follow on safety study of patients who have completed randomised Phase II and III studies, and Study A3921041 was an ongoing study of Japanese subjects primarily to assess long term tolerability and safety with a secondary objective of assessing ongoing efficacy conducted in subjects who had completed Studies A3921019, A3921025, A3921032, A3921035, A3921044, A3921045, A3921046, A3921064, A3921069, A3921073, A3921109, A3921039, and A3921040. The efficacy outcome measures were ACR20, ACR50, ACR70, HAQ-DI score and DAS28-4(ESR).

Study A3921041 was a long term safety and tolerability study with efficacy as a secondary outcome, undertaken in Japanese patients and the dose could be increased from 5 to 10 mg; if the dose had been increased to 10 mg and was taken continuously for < 84 days, that person was included in the 5 mg group. If the higher dose had been taken for > 84 days at the cut-off, the subject was included in the 10 mg cohort.

At A3921024 enrolment, initially all patients were commenced on 5 mg with the scope to increase the dose to 10 mg improve control of the RA at the discretion of the investigator. Following an amendment, from June 2009 10 mg bd was the enrolment dose (with the exception of subjects in China), with an option to decrease to 5 mg bd for safety reasons. This resulted in much larger number of patients on the 10 mg dose at the new cut-off of April 2012, but not much longer term exposure overall at this 5 mg dose which is of limited relevance for the current proposed indication.

Comments: this amendment has had significant impact for the assessment of both safety and efficacy of the 5 mg dose, which is the proposed dose in this application. All patients outside of China will be allocated to 10 mg bd, removing any long term data for the 5 mg group coming out of trials including the final pivotal trial, A3921069.

The dose taken in the long term extension studies is not necessarily the same dose the patient received in the Phase II or III trial. Traditional DMARD usage was permitted but not bDMARD (washout required). The baseline data about concomitant medications used was taken from the entry point into the Phase II or III trials.

[52] This was an unsolicited manuscript prepared by the sponsor for submission (neither peer-reviewed nor accepted for publication) in lieu of 2 year data for the pivotal efficacy trial submitted in Round 3. The data underpinning this manuscript was not available, preventing a detailed evaluation; and this is not a trial designed to demonstrate safety and efficacy for the proposed indication.

Updated safety summaries were provided for the Third round of evaluation with an April 2012 cut-off, and in response to the Delegate's initial Overview of 29 August, 2013 (see above) with a cut-off of April 2013, but there was no updated efficacy summary, thus the following is taken from the March 29 2011 cut-off, supplied with the initial submission.

In total, 3227 subjects were included: 1321 treated with tofacitinib 5 mg bd and 1906 treated with 10 mg bd. Of these, 2019 were also on background DMARDs and 1208 were on tofacitinib monotherapy as determined by their first baseline study entry prior to the extension trial. 83% were women, the age range was 18 to 86 years (mean age of 53), and 16.8% were 65 or older.

At the cut-off date of 29 March 2011, there were 1022 (77%) subjects ongoing in the 5 mg group and 1768 (92.8%) in the 10 mg. In the total group there were 970 subjects treated for more than 12 months, 659 for more than 24 months and 62 for more than 36 months. At the cut-off date, 25.7% had discontinued in the 5 mg group on background DMARDs (as defined at entry to very first Phase III study) and 18.8% in the monotherapy group. Efficacy (as measured by ACR20, ACR50 and ACR70), reduction in HAQ-DI and DAS28-4 appeared to be maintained for up to 3 years, but there was migration to the 10 mg dose in both studies which makes interpretation difficult, as they were only included in the 10 mg group if they had been taking that dose > 84 days. The ways in which those not continuing are imputed in the long term study is not clear: if not included, then by definition, those remaining would be those continuing to respond.

Study A3921041 showed a significant decline in numbers over the time period with 337 subjects at week 2, and just 8 subjects at the 36 month assessment in the 5 mg group. Overall, for the combined studies, in the 5 mg group the median duration of exposure was 21 months but there were relatively few beyond 33 months. When taking concurrent DMARDs, the median duration of exposure to tofacitinib decreased further to 12 months. Only 5 patients continued beyond 21 months on the 10 mg dose level. It is unclear whether these declining numbers reflect discontinuation due to intolerance, AEs and/or a loss of efficacy.

Comments: the 5 mg group is significantly confounded by the prior treatment received before entry into the long term extension studies. The initial ongoing response rates may reflect the impact of prior higher dosing levels in the Phase II trials (up to 30 mg), and in the Phase III trials (5 and 10 mg). The group in whom efficacy in controlling signs and symptoms was demonstrated in the Phase III trials were taking concurrent DMARDs: the median duration of treatment in the long term extension study of this group was 12 months which might reflect waning efficacy on that combination at the lower tofacitinib dose and/or discontinuation due to intolerance and/or AEs.

Additional comment on the long term extension studies: Completion rates were highest of all in the studies where tofacitinib was used as monotherapy (in short term studies), rather than in combination; in the longer term studies, the median duration of combination with DMARDs was 12 months compared with 21 months for monotherapy. Both findings suggest tolerability is better as a single agent.

Vaccine studies

Study A3921129 and Vaccine Sub-study A3921024 were carried out primarily to determine the response rates to immunisations with pneumococcal and influenza vaccines.

Comments: these trials used a higher dose of tofacitinib (10 mg bd) than now being sought for registration, which might be expected to inhibit the development of a humoral response more significantly. The relevance and generalisability of these results is uncertain for those patients taking tofacitinib 5 mg bd.

Summary and discussion of efficacy

The fundamental questions are:

1. Has efficacy as monotherapy been demonstrated? If so, is this demonstrated for the proposed second line indication?
2. Has efficacy in combination with other DMARDs including MTX been demonstrated? If so, has this been demonstrated for the proposed second line indication?
3. whether the efficacy of tofacitinib 5 mg bd has been adequately established in the population in which the indication is being sought
4. If not, is there a clearly identifiable population where efficacy has been demonstrated?

These questions are addressed under *Risk-benefit analysis*, below.

Limitations of methodology

These are addressed in detail for each trial above.

Data deficiencies

The sponsor proposed second line use of tofacitinib which in the Australian context would mean potentially after prior tDMARD therapy. There was no direct comparison with proven bDMARDs to demonstrate superiority, or non-inferiority, only inferences of the relative efficacy of tofacitinib compared with adalimumab can be made, and therefore, whether it should be used after a single tDMARD failure or intolerance as proposed by the sponsor is not certain. Additionally, the comparative safety profile with bDMARDs has not been established.

Patients with severe renal impairment or moderate to severe hepatic impairment were excluded from the five of the Phase III trials and those with moderate renal failure were excluded from the most recently conducted trial (A3921069). Given the PK effects observed in the earlier phase trials and the rise in creatinine observed in the trial participants, there is no safety data to support use of tofacitinib in those with these conditions.

The number of subjects over the age of 65 randomised to receive treatment ranged from 10-17%. This may be due to failing screening, especially with the increased likelihood of comorbidities and laboratory test abnormalities (such as impaired renal function) but as a consequence, there is relatively limited safety and efficacy data available for this population. With the numbers enrolled, it would not be possible to perform a subset analysis.

The sponsor is currently planning a comparative study with bDMARDs (A3921133). The primary objective of this study is to evaluate the safety of tofacitinib at two doses (5 mg bd and 10 mg bd) versus a TNF inhibitor; the co-primary endpoints are adjudicated major adverse CV events and adjudicated malignancies excluding non-melanoma skin cancers during study participation. Secondary safety endpoints will include adjudicated opportunistic infections and other safety events. It is anticipated that approximately 4000 patients will be enrolled; the randomisation scheme will yield a ratio of 1:1:1 (tofacitinib 5 mg bd: tofacitinib 10 mg bd: TNF inhibitor). Recruitment is expected to occur over 3 years and the total duration of the study will be approximately 5 years after the first subject is randomised (estimated completion date 2022). The Study Protocol is under review with the US FDA and will be provided to the TGA prior to the commencement of the study.

Safety

In the initial submission, using a cut-off of March 29 2011, the total number of subjects (patient-years) exposed to tofacitinib was 1369 (419.95) in Phase II studies, 3030

(2210.97) in the Phase III studies, 3227 (3085.13) in long term extension studies, and 4816 (5716.03) in all of these studies combined. In the open label, long term safety study, 1321 subjects have been treated with tofacitinib 5 mg bd and 1906 were treated with 10 mg bd. In the long term extension studies, there were 970 subjects treated for more than 12 months, 659 for more than 24 months and 62 for more than 36 months.

In the submission for the Round 3 clinical evaluation in response to the CHMP's negative opinion, the sponsor submitted an updated summary of safety entitled *Safety Summary to Support Structure Supplemental New Drug Application* with a cut-off of 19 April 2012. This included a new analysis set of patients defined by the dose they had received, and the trials they are drawn from, characterised as follows:

- long term extension (LTE), comprised those receiving either dose level (subdivided further according to dose = LTE 5 mg or LTE 10 mg) only while in the extension studies, that is, excluding consideration of their prior trial dosing level which may have been higher for those now on 5 mg in the long term extension 5 mg group
- P2P3LTE = Phase II, Phase III + LTE Phase II, III for both doses combined
- P2P3LTE 5 mg bd = patients who had only ever received 5 mg from their first dose in either the Phase II or III or LTE (that is, a distinct subset of P2P3LTE who have never received a dose other than 5 mg)
- P2P3LTE 10 mg bd patients who had only ever received 10 mg from their first dose in either the Phase II or III or ≤, that is, a distinct subset of P2P3LTE who have never received a dose other than 10 mg

Comments: The most relevant group for understanding the safety and tolerability of longer term use of tofacitinib 5 mg bd as proposed for registration should be the P2P3LTE 5 mg bd group presented in the Updated Safety Summary (cut-off April 2012). This group has only ever had 5 mg, unlike the LTE 5 mg group who were allocated 5 mg dose regardless of prior treatment dose (a significant confounding factor affecting efficacy assessment and to a lesser extent, safety assessment). The P2P3LTE 5 mg bd is a subset of patients who have never received a dose other than 5 mg, and is drawn mainly from patients continuing on from the more recent Phase III trials. While this means there are numerically more patients, there is a much lower duration of treatment per patient: a total of 1955 patients (2174 patient years). However, the sponsor did not describe how long they had been treated in the 5 mg group (that is, how many patients had received tofacitinib > 6 months, > 12 months, > 18 months and so on), nor the median duration or range of treatment time, making it difficult to assess the safety effect over time on the 5 mg treatment dose, the impact of discontinuation rates, etcetera. In addition, this new cohort definition was introduced for the Third round evaluation, but a subsequent update in the Round 4 submission reverted to the previous LTE definition, making comparisons of safety and efficacy in this group over time difficult.

In the LTE 5 mg group, there were 1421 patients, representing a total exposure of 3243 patient-years. The amendment changing the dose to 10 mg on entering the extension studies from June 2009 (apart from subjects in China who received 5 mg bd) meant there was an absolute net increase in total numbers of only 100 subjects (1421 compared with 1321 in LTE) between the cut-off dates of March 29 2011 and April 12 2012. Over the next 12 months, a further net increase of only 31 (1421 to 1453) occurred (April 2013 cut-off date).

Thus the focus of the longer term analysis is on the patients taking 5 mg in the long term extension studies for who the clearest amount of information is available over time, despite there being the issues of differing dose levels prior to the long term extension enrolment.

Table 38: Incidence rates (events/100 patient-years) for Safety Events of Interest, tofacitinib 5 mg bd and 10 mg bd cohorts, in the ongoing open label populations study. Data taken from updated Integrated Summary of Safety.

Parameter	**5 mg BID Cohort** N = 1955 Exposure = 2174 pt-yr Incidence Rate (95% CI) [number of pts with event]	**10 mg BID Cohort** N = 1846 Exposure = 2460 pt-yr Incidence Rate (95% CI) [number of pts with event]
Serious Adverse Events	10.16 (8.87, 11.63) [210]	11.13 (9.86, 12.57) [261]
Adverse Events Resulting in Discontinuation	7.87 (6.77, 9.14) [170]	9.18 (8.05, 10.47) [223]
Mortality (deaths within 30 days of last dose)	0.28 (0.12, 0.61) [6]	0.20 (0.09, 0.49) [5]
Serious Infections	2.73 (2.11, 3.52) [59]	3.56 (2.88, 4.39) [87]
Tuberculosis	0.092 (0.023, 0.37) [2]	0.37 (0.19, 0.70) [9]
Opportunistic Infections*	0.46 (0.25, 0.86) [10]	0.65 (0.40, 1.06) [16]
Herpes Zoster	4.00 (3.23, 4.95) [84]	4.75 (3.95, 5.71) [113]
Malignancies (excl. NMSC)	0.83 (0.52, 1.32) [18]	0.94 (0.62, 1.41) [23]
Lymphoproliferative Disorders/Lymphoma	0.046 (0.006, 0.33) [1]	0.081 (0.020, 0.33) [2]
Composite MACE (adjudicated)†	0.50 (0.22, 1.11) [6]	0.36 (0.18, 0.72) [8]

Subject exposure time is the sum of the tofacitinib exposure from the index study and the tofacitinib exposure from the LTE study. Some events may have occurred post end of treatment, these events were counted in the numerator and subjects' full tofacitinib treatment exposure was included in denominator.
BID=twice daily; CI=confidence interval, N=number of patients; NMSC = nonmelanoma skin cancer, MACE = major adverse cardiovascular event; N=number of patients; P2P3LTE=Phase 2, Phase 3, and long term extension studies; pt-yr=patient years; pts=patients
* Opportunistic infections including tuberculosis
†Composite MACE is from the Phase 3/LTE cohort only (5 mg: N=1530, exposure=1203 pt-yr; 10 mg: N=1512, exposure=2215 pt-yr) as the adjudication of cardiovascular events began in the beginning of Phase 3 program, and did not include patients in the Phase 2 studies.
Source: (19 April 2012), P2P3LTE Tables 485.3.1, 485.3.2, 485.3.3, 485.3.4, 485.3.5, 485.3.6, 485.3.7, 485.3.8, 485.3.9, 485.3.10.

In response to the Delegate's initial Overview of 29 August, 2013 the sponsor submitted an updated table of "*Cumulative Incidence rates for selected safety events of interest in Phase III Controlled and Long term extension studies: tofacitinib 5 mg bd and Placebo*". This reverted to considering the populations by LTE 5 mg (subset of Group 1) which is updated to longer term data, alongside the very much shorter term data (not updated) for those in Phase III studies separately, with the 'placebo' group also reported for these studies (see Comment below). The following data deficiencies for the LTE 5 mg group severely limit the ability to consider the information:

- No data or supportive explanatory text to support this updated table were provided to permit an evaluation;
- Incomplete important fields, such as AEs leading to discontinuation, gastrointestinal perforation;
- No absolute numbers for any of the AEs including deaths;
- No break-down of duration of therapy for this patient group.

Comment: the Delegate did not consider the Phase III data provided in this table for comparative purposes for the following reasons:

- The Phase III data appear to be old and to have been superseded (that is, this is not an updated safety summary: updated efficacy and safety data for Study A3921044 were

provided for evaluation with the latest submission, but this was not incorporated into this *Safety Summary Update*);

- The absence of a cut-off date for when the Phase III data were assessed adds to the lack of clarity with this submission;
- The term 'placebo' without qualification implies a control arm with no treatment; however, patients in that group crossed to active treatment after 3 months in many studies, and by 6 months in all studies. As previously mentioned the placebo group was of no value in establishing comparative safety and efficacy beyond 3 months in 2 studies and limited for the other 3 studies, and of no value beyond 6 months.

Table 39: Duration of exposure to any dose of tofacitinib in the P2P3LTE population

Duration of Exposure (months)[a]	No. of Patients	Duration Interval (months)[b]	Patient-Years for Duration Interval[b]
≥1	4816	<1	395.93
≥3	4664	≥1 - <3	740.17
≥6	4213	≥3 - <6	1014.48
≥12	3768	≥6 - <12	1668.35
≥18	2703	≥12 - <18	889.26
≥24	905	≥18 - <24	385.21
	696	≥24	622.73
Total patient-years[c]			*5*16.03*

a Exposure is to any dose of CP-690,550. One month was defined as 30.25 days.
b Patient-years in each of the duration of exposure rows is incremental and unique; thus does not include the duration (years) of previous time intervals. Patients are counted only once if they participated in both Ph 2 or 3 study and also a long term extension (LTE) study, however their time in both the qualifying and LTE study is included in the person time column.
c Total patient-years is the sum of patient-years for each duration interval.
Studies included: A3921019, A3921024, A3921025, A3921032, A3921035, A3921049, A3921040, A3921041, A3921044 (data up to 1 year), A3921045, A3921046, A3921064.
Source: RMP Table 2.1

Adverse events

Shorter term controlled pooled safety data was available for the Phase III background DMARD studies (A3921032, A3921044, A3921046 and A3921064). The protocols and demographics are summarised for each trial in the *Efficacy* section, but each had a control DMARD arm and Study A3921064 had an adalimumab arm also.

The numbers of patients with AEs up to 3 months were similar between the 5 mg, placebo and adalimumab arms. Between 3-6 months, the number of AEs in the 5 mg and 10 mg groups increased (39.7% and 37.5%, respectively) compared with the placebo (26.2%) and adalimumab (33.3%) groups. Temporary discontinuations or dose reductions were more common in the 5 and 10 mg groups (7.5% and 6.6% respectively) compared with placebo (1.8%) or adalimumab (4.9%). It is not possible to compare with a placebo response as all subjects had commenced tofacitinib, but above 6 months there were still more temporary discontinuations or dose reductions in the tofacitinib 5 and 10 mg arms at 6.5% and 8.1%, respectively) than adalimumab (2.9%). The percentage discontinuing due to an AE was similar across the arms.

Up to 3 months, with the 5 mg dose, there were more gastrointestinal disorders (16% versus 12% in placebo, 10.3% in adalimumab), infections (20.9% versus 18.2% in placebo, 10.3% in adalimumab), headache (4.2% versus 2.1% in placebo and 2.5% in adalimumab) and hypertension (1.8% versus 0.9% in placebo, 0 in adalimumab).

From 3-6 months, the trend was maintained with more infections (17.9% for 5 mg tofacitinib, 9% placebo, 13.7% adalimumab). The individual statistics for hypertension and headache were not presented but stated to be below 2% (see *Comment* below).

The number in the placebo arm dropped from 559 to 221 at month 3 as there was mandated crossing in Trial A3921032 and early escape in the other 3 trials, with the remainder joining the tofacitinib arms at 6 months.

Comment: With transfer and depletion of the placebo arm, it is impossible to make meaningful comparisons with the tofacitinib arm after month 3. Similarly, comparisons with the adalimumab arm after month 3 should be interpreted with caution as adding in

patients with no exposure and lower AE rates from the control population to the tofacitinib arms would lead to an underestimate of event rates for tofacitinib. It also prevents an analysis of event rates over time with tofacitinib.

Two year safety data were supplied for Study A3921044 at the Round 4 stage. All subjects in the placebo arm crossed to tofacitinib at month 3, but the data is presented for these groups separately and by dose level, allowing analysis of discontinuation and AEs rates for the 5 mg dose level.

The most frequent AEs (≥ 2%) in the 6-24 month period were those previously identified: infections (herpes zoster 4.6%, pneumonia 2.3%, upper respiratory tract infection 5.9%, urinary tract 3.1%), abnormal LFTs (6.6%), anaemia (1.3%) and hypertension (1%).

The cumulative rates for the 24 month period were: SAEs 8.1%, DAEs 11.8%, and 21.4% required a temporary discontinuation (dose reduction not allowed).

Table 40: Treatment emergent AEs treatment related by treatment sequence for tofacitinib 5 mg from day 1 (that is, not including placebo) in Study A3921044*.

No (%) pts in the trial at that time	0-3 months	3-6 months	6-24 months
AEs	30.5	27.8	52.3
SAEs	0.9	1.3	5.9
Severe AEs	3.1	1	4.6
Discontinued due to AE	3.7	1.9	6.2
Temporary discontinuation due to AEs	3.7	4.2	13.5

*Taken from, and recalculated by Delegate, Tables in Module 5.3.5.1, Round 4)

Comment: the data for AEs and discontinuations between time intervals has been calculated at each point using the full analysis set, without censoring those who have discontinued. Therefore the event rates for all time points after the first will be an underestimate as those no longer participating are still being counted. The data presented for the 2 year A3921044 study in Table above has been recalculated to reflect discontinuations from the previous interval. It is difficult to determine whether this has occurred with other consecutive time point analyses as there are no other studies with the same population carried forward to check (all had crossing from the placebo arms). If so, it would lead to an underestimate of all the AE reporting which would become larger with longer trial duration.

The safety data for monotherapy Study A3921045 (tofacitinib versus no treatment, controlled for 3 months) was included in the initial submission and a 12 month safety report for Study A3921069 (tofacitinib versus MTX) was submitted separately at Round 3. Comparisons were possible for Study 1044 up to 3 months, and there were similar rates of TEAEs and discontinuations across treatment and placebo arms.

For study A3921069, the AEs with ≥ 2% incidence were presented for tofacitinib and MTX. The risk of infections overall were the same, but with tofacitinib, there were more cases of bronchitis (3.8% compared with 0.5% for MTX) and herpes zoster (2.2% compared with 1.1%). Higher AE rates for tofacitinib were seen for hypertension (4.3% compared with 1.6%), hypercholesterolaemia (2.2% compared with 0.5%), weight gain (2.7% compared

with 0.5%) and increased creatine phosphokinase (2.4% compared with 0.5%). With tofacitinib there were lower rates of alopecia (2.4% compared with 2.7% for MTX), LFT abnormalities (2.4% compared with 7%), nausea (17.7% compared with 5.4%) and diarrhoea (7.5% compared with 3.5%). Higher rates of gastritis and abdominal pain occurred with tofacitinib (2.2 compared with 1.6%; 3% compared with 1.6%, respectively).

Comment: Study A3921069 AEs demonstrated the well-known side effect profile of MTX and showed a lower incidence of nausea, diarrhoea and abnormal LFTs with tofacitinib. While the risk of infections was similar, those on tofacitinib had higher rates of bronchitis and herpes zoster, increased risks associated with an adverse cardiac risk profile (hypertension, increased cholesterol, and weight gain). The significance of the increased CPK is uncertain.

In the long term extension studies, the most common TEAEs were: nasopharyngitis (10%), upper respiratory tract infection (7.3%), urinary tract infection (4.6%), hypertension (4.2%), bronchitis (4.5%), back pain (3.3%), influenza (3.3%), herpes zoster (4.1%), headache (3.7%), diarrhoea (3.4%), sinusitis (2.8%), and RA (2.4%). The most notable AEs included: a significant number of infections, particularly upper respiratory and urinary tract infections, tuberculosis (including disseminated TB), opportunistic infections and herpes zoster reactivation. Other AEs included malignancies, hypertension (7%), hypercholesterolaemia and hyperlipidaemia, a rise in creatinine levels, haematological abnormalities (leucopenia, neutropenia and anaemia), gastric perforations and ulcerations.

The TEAE rate in the 5 mg group was 47.3 new events/100 patient-years compared with the 10 mg dose at 124.9 new events/100 patient-years. Where higher tofacitinib doses were added to background DMARDs in the Phase II studies, there were many more AEs in the tofacitinib group (37 in 546 subjects compared with 0 in the control arm), particularly infections and haematological events (anaemia and leucopenia). In the Phase II monotherapy studies, 736 patients were treated with tofacitinib and there was an adalimumab comparator arm (53 patients) and placebo (176 patients). However the numbers were small, especially after 3- 6 months making comparisons difficult.

Comment: this much higher AE rate for the 10 mg dose, together with the lack of significant additional efficacy, was one of the pivotal arguments for refusal of that dose in the Delegate's initial Overview of 29 August (see above), following which the sponsor withdrew it from consideration for registration. It indicates though that caution must be exercised in any patients groups identified where metabolism or clearance might be altered, such as in drug interactions, hepatic impairment, renal impairment, and ethnographic differences (the Cmax and AUC were higher in Asian women, and infections especially herpes zoster rates are higher in this group).

Serious adverse events and deaths

Comment: the *Updated Safety Summary* included in the Round 3 submission to the TGA does not provide absolute numbers of events or deaths as a running total since the commencement of the program, and no information about absolute numbers of deaths is included in the April 2013 update. Rather, where actually provided, the sponsor reports the new additional events or deaths in isolation, to be added to the previous total. This creates significant difficulties in tracking deaths and on which dose they occurred.

Deaths

Thus, the totals are calculated using the CHMP final assessment report, and adding in the updated safety data from Round 3. In the updated *Table of Adverse Events* submitted in response to the Delegate's initial Overview (29 August 2013), no absolute number of deaths was provided. In the last two submissions with two updated safety summaries,

there is an all-cause mortality rate and cumulative mortality rate up to 30 days of last dose for exposure to tofacitinib in the development phase (P2P3LTE), but no all-cause rate for any tofacitinib exposure.

At the March 29 2011 cut-off: 34 deaths in tofacitinib treated patients were recorded (12 in Phase III studies and 22 in the long term extension studies), with one each in the comparator and adalimumab arms. Twenty deaths occurred within 30 days of discontinuation of the study drug.

By the April 2012 cut-off, an additional 11 deaths in the long term extension studies had been reported: 5/11 cases were receiving the 5 mg dose. Four deaths were from pneumonia/sepsis and 7 from malignancies. The CHMP Final Assessment Report identified an additional 4 deaths which were not considered related to the study drug by the investigators: 2 cancers, 1 pneumonia, and 1 patient had a cardiac arrest a week after being diagnosed with pneumonia. The Delegate is in agreement with the CHMP report that a possible causality for tofacitinib cannot be excluded for these deaths.

Two additional deaths were reported and attributed to adalimumab, thus the total deaths are 45 in the tofacitinib treatment groups, 3 in the adalimumab group and 1 in the placebo group (possibly on tofacitinib at the time of treatment). The duration of exposure to tofacitinib is far greater but the death rate remains notable, and particularly the causes of death.

The previously calculated incidence rate of 0.641 deaths/100 patient-years (at March 29 2011) increased to 0.648 (95% CI 0.422-0.993)/100 patient-years.

Serious adverse events

Analyses of the SAE rates for Phase III studies: comparisons with placebo can only be made in the Phase III studies up to the 3 month mark, due to the mandated crossing and early escape trial design. The rates were similar at 3.1% and 2.7% for 5 mg and 10 mg, respectively, and 3.5% for placebo.

In the LTE studies, the SAE rates were 16% in the 5 mg group and 6% in the 10 mg group: of 102 SAEs, 45 were infections (23 pneumonia, 8 herpes zoster (7 in the 5 mg group), 8 UTI, 6 cellulitis), 50 were cancers and 7 were cholelithiasis.

Infections

Pneumonia was the most common serious infection (requiring hospitalisation or parenteral antibiotics), and together with herpes zoster was the most common infective SAE leading to discontinuation. Other common serious infections included skin and soft tissue infections. Opportunistic infections occurred including viral (cytomegalovirus (CMV), multidermatomal herpes zoster, BK encephalitis), fungal (cryptococcus, oesophageal candidiasis, pneumocystis pneumonia). Disseminated opportunistic infections including cryptococcal meninigitis, TB, Pneumocystis jiroveci, and CMV occurred at much higher rates than in the control or adalimumab population. 12 such cases developed on the 5 mg dose being sought for registration.

Nine deaths from infection including 8 from pneumonia occurred during the Phase II, III and long term extension studies at the March 29 2011 cut-off: 6 of these occurred on the 5 mg dose, 1 with 3 mg and 2 with 10 mg. An additional death from infection (pneumonia) was reported for the updated April 2012 cut-off. One death from infection was observed in the 'placebo' group (though it unclear whether this patient was by then receiving tofacitinib).

In the pivotal studies which utilised the doses being sought in this application, one in three of the trials where tofacitinib was added to MTX (A3921064) yielded an increased rate of serious infections in the tofacitinib groups compared with placebo or adalimumab; in the other two trials, the rates did not vary between the treatment arms (A3921032,

A3921044). Where tofacitinib was used as monotherapy, there were 11 serious infections: three in the 5 mg group and eight in the 10 mg group. For those receiving 5 mg or 10 mg doses of tofacitinib bd compared with MTX (A3921069), there were more AEs, (including SAEs) in the MTX arm than either of the tofacitinib arms. The SAEs in the tofacitinib arms were predominantly infections, including pneumonia, herpes zoster, 3 cases of tuberculosis including disseminated TB, TB infection in the bone, chronic bronchitis, Dengue fever and typhoid.

In the sponsor's response to the Delegate's initial Overview, the cumulative incidence rates for selected safety events of interest in Phase III and tong term extension studies are presented, including serious infections, herpes zoster and opportunistic infections. No conclusions can be drawn about long term safety with this dose as no data are presented on outcomes by the median duration of treatment in the long term extension studies. In the Phase III trials, it is not clear whether the tofacitinib treatment arm in the table includes those who ever received tofacitinib (that is, includes those who crossed over after the stipulated time on placebo) or whether these patients were still included in the placebo arm once they had commenced tofacitinib (which could potentially increase the toxicity observed in this arm).

Herpes zoster

From the April 2012 cut-off, 346 cases had been reported including a case of disseminated multidermatomal herpes zoster. The incidence (per 100 patient-years) of herpes zoster events amongst those in the P2P3LTE 5 mg bd group was 4.00 (95% CI 3.23, 4.95) which is similar to the 4.4 reported in the 5 mg arm of the 2 year study report for A3021044. In the LTE for both doses, the rate is higher at 4.27 (95% CI 3.85, 4.75) which includes the 10 mg dose level. Both these levels are much higher than reported for anti-TNFα therapies including etanercept 0.89 (0.56, 1.33), infliximab or adalimumab 1.11 (0.79, 1.51) or nonbiological DMARDs 0.56 (0.36, 0.83) (Strangfeld et al,[53] JAMA 2009). Risk factors were increasing age, and more cases occurred in the extension studies.

In response to the Delegate's initial Overview, the sponsor submitted a safety meta-analysis in support of the 5 mg bd dose for serious infections, including herpes zoster, compared with a range of approved biologic DMARDs including, infliximab, rituximab and adalimumab. This meta-analysis was conducted by the sponsor, has not been peer-reviewed, and is not published other than in abstract form. The inclusion of just serious infections (multidermatomal or ophthalmic) dramatically reduces the number of herpes zoster infections that occurred in the studies and both down plays the significant morbidity and potential complications of this condition, and reduces the appearance of this risk. There is considerable morbidity and after pneumonia, herpes zoster was the next most common infection-related reason for discontinuation. The confidence intervals for the adalimumab arm reflects the low numbers in the Trial A39121064, the relative rarity of the events described and is not a substitute for a randomised controlled trial designed specifically to compare the safety and efficacy of an established bDMARDs with tofacitinib.

The *Updated Safety Summary* identified a total of 16 cases of tuberculosis have been reported including 2 cases of disseminated TB; 10 cases were pulmonary, and 6 extra-pulmonary, of which 2 were disseminated. Five patients were taking the 5 mg dose and 11 were on the 10 mg dose level. The AE reports indicate that the condition has not resolved fully for some of the severe cases, or for the four patients reported in the April 2012 update.

Twenty-five additional opportunistic infections occurred as follows (CMV (6 cases), multidermatomal herpes zoster (2), BK encephalitis (1)), fungal (Cryptococcus (3),

[53] Strangfeld A. et al. Risk of Herpes Zoster in Patients With Rheumatoid Arthritis Treated With Anti–TNF-alfa Agents. *JAMA* 2009;301(7):737-744

oesophageal candidiasis (8), pneumocystis pneumonia (3)) and non-TB Mycobacterial pulmonary infection (2). The patient with disseminated CMV has not made a full recovery and others are reported as still recovering. Given the Pneumocystis infections, a case could be made for PCP prophylaxis.

Malignancies

As of April 2012, 86 non-melanoma skin cancer malignancies have been reported. Lung cancer was the most common malignancy. Three lymphomas were reported in the P2P3LTE, and a case of acute myeloid leukaemia was notified to the TGA, occurring in August 2013. An increased incidence of both types of cancer are seen in those who are immunosuppressed, therefore it is not possible to exclude a causative role for tofacitinib, either in development or acceleration of the growth of the tumour. In the estimate of incidence for all cancers except non-melanoma skin cancer, the rate increased over time from 0.785 (95% CI 0.488-1.263) at 0-6 months to 0.974 (95% CI 0.587-1.615) at 12-18 months to 1.42 (95% CI 0.59 -3.4) at 30-36 months strongly suggesting an increased risk with duration of therapy.

In the *Updated Integrated Summary of Safety* (Third round clinical evaluation), there appeared to be an increased risk of lymphoma compared to the background US population, that was dose related. The sponsor estimates the overall incidence rate for lymphoma was 0.070 events/100 patient-years (95% CI: 0.034, 0.148), and the standardised 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 100 patient-years for 5 mg compared to 0.081 (0.020 to 0.33) per 100 patient-years for 10 mg. In the response to the Delegate's initial Overview, the sponsor states that this may be due to the background risk in the RA population; while this is true, it is noted in the PI for adalimumab that malignancies, including those associated with immunosuppression, emerged after a median treatment time of 30 months. A pattern of increasing incidence is emerging over time with duration of exposure.

Two cases of malignancy reported to the TGA, occurring in August 2013 give rise to concern. In one, a subject in their 70s who had received 10 mg bd in the long term extension study for 3 years underwent excision of 4 basal cell carcinomas, 6 squamous cell carcinomas and 6 solar keratoses. The development of such a large number of skin cancers in a single individual at one time raises concerns about the impact of immunosuppression and the risk of developing multiple skin cancers, observed with other immunosuppressive agents such as ustekinumab. A prior history indicated a solar keratosis years earlier in this subject, indicating a predisposing risk factor, but increased sun exposure and such risk factors are common in the Australian population. In the other case, a subject in their 50s reported the appearance of a freckle changing over time after commencing tofacitinib (dose blinded) which when excised was a melanoma. All the cancer types here are associated with immunosuppression and a causative role for tofacitinib in their development or growth rate cannot be excluded.

Cardiovascular related safety issues

Cardiovascular events: In the P2P3LTE, 2.6% had a myocardial infarction in the 5 mg group and 1.1 in 10 mg group, and cerebrovascular disease was reported in 0.5% and 0.4% in 5 and 10 mg groups, respectively. A lower incidence of major adverse CV events and a small increase in rates of congestive heart failure was noted in the tofacitinib arm compared with the adalimumab arm but given the relatively low numbers of subjects and events, these findings should be interpreted with caution. In the updated safety table for the LTE 5 mg bd group provided for the Round 4 evaluation (cut-off date April 2013), there is a rise in MACE incidence rate compared with the previous cut-off 12 months earlier (0.34

(95% CI 0.19-0.6) compared with 0.29 (0.15-0.58) but no supporting text nor data were provided to account for this.

Dyslipidaemia: In the long term extension studies, 9.6% and 3.6% had dyslipidaemia on 5 and 10 mg bd, respectively, which equates to 4.2 and 6.1 new events/100 patient years respectively when standardised for duration of exposure to tofacitinib. THE LDL-C, HDL-C and total cholesterol levels increased 14.2%, 15.5%, 12.7% with 5 mg tofacitinib within 3 months of commencement and remained elevated. The evidence for dose-related dyslipidaemia is more compelling, with reports of increased LDL-C and triglycerides.

Elevated LDL-C (around 20%) was observed in the early studies with doses as low as 1 mg, and appeared to be dose-dependent. In the pivotal efficacy studies with tofacitinib in combination with MTX or as a single agent, dyslipidaemia was reported in more patients receiving tofacitinib than placebo and the incidence peaked at the 10 mg dose. A secondary PD study (submitted in response to the CHMP questions regarding safety) has suggested that this is in part due to the reversal of the catabolic cholesterol ester seen in those with RA. However, the observed increase and absolute levels on tofacitinib were not only higher than the placebo group but also higher than those on adalimumab plus MTX arm of study A3921064, suggesting this may be more than just an effect of reversing the underlying disease process. In one study, the addition of atorvastatin in the group receiving tofacitinib reversed the dyslipidaemia.

Hypertension: In the P2P3LTE group, 7.8% of patients in the 5 mg group and 2.9% in the 10 mg group developed hypertension (a risk of 4.4/100 patient-years for 5 mg and 5.5 new events/100 patient years for the respective doses). Discontinuations due to Grade 4 hypertension were rare, but two deaths due to hypertension occurred. The mechanism for this is not clear, and may relate to the rise in creatinine which is presumed to be due to renal dysfunction. This is not a noted side effect of bDMARDs.

Weight gain: Weight gain was reported as an AE, most notably in the sixth pivotal trial where a mean gain of 2 kg was reported at 12 months. Given there were already patients with significantly elevated body mass indices listed in the demographic summaries, this poses an additional risk for CV disease.

ECG studies: In Study A3921069, ECG safety study was one of the safety endpoints but was not included for evaluation at Round 3. The subsequent submission of an ECG summary, in response to the clinical evaluator's request for the data, indicated a potential incidence of QTcF in the tofacitinib arm compared with the MTX. This led both the clinical evaluator and the Delegate to withdraw any support for consideration of approval for registration until data were supplied for evaluation. The sponsor has provided summary tabulations for the mean increase in QTcF from baseline to final visit by study for the development program, and the number and proportion of patients with QTcF ≥ 60msec. The 2 year ECG safety data Study A3921044 were supplied after a further request from the clinical evaluator.

The clinical evaluator concluded that the patients with ECG prolongation often had concomitant medications or underlying conditions that might explain the QTc prolongation.

The clinical evaluator considered that the studies indicate no issues up to 24 weeks of treatment but in studies of 6 months or longer there are some increases in mean QTcF and in the proportions of subjects with QTcF ≥ 60msec. The changes were considered "no worse" than for MTX but also that a cumulative toxicity could not be discounted and had not been addressed by the sponsor's response.

It was of significant concern to see a patient on 5 mg bd tofacitinib in Study A3921069 with an abnormal ECG (QTcF 500 msec) at baseline had no further recordings available ("not calculated") at the Year 1 and 2 visits. Safety, including performing ECGs, was a

secondary endpoint for this study. Data for 4 patients were missing at the Year 1 visit and then subsequently found to have a prolonged QTcF > 500msec at a visit a year later.

It is also of significant concern to the Delegate that the sponsor provided the following explanation for not reporting an abnormal ECG result as part of the A3921069 ECG safety summary: *"Two patients …reported a QTcF increase of ≥ 60 msec in an unplanned reading but were not included in the ECG summary since the unplanned result was not the last value prior to a visit."* This explanation appears to demonstrate a misunderstanding of the purpose of safety studies, which are to record events for analysis to ensure safety, and this raises concerns about the potential for other important data to be omitted on such dubious grounds.

The patient profiles indicate some variable and concerning attribution as to whether abnormal ECGs are clinically relevant. In Study A3921069, a woman in her 60s on 5 mg bd tofacitinib was admitted with chest pain, had ECG demonstrating QTc prolongation and an episode of "circulatory collapse", and the ECG taken and findings at that time were not considered relevant.

Comment: Overall, the following were not considered acceptable:

- the reason not supplying abnormal ECG data obtained outside a planned visit in 2 patients;
- not doing or recording an ECG at either of the two consecutive pre-specified timepoints when a baseline abnormality has been detected;
- not doing or recording ECGs at the requisite timepoints, especially as 4 patients had abnormal QTcF recorded a year later;
- the possible potential for cumulative toxicity raised by the clinical evaluator to explain the increase in QTcF beyond 6 months in a proportion of patients in the Phase III studies.

Otherwise, the sponsor's responses were considered adequate and the likelihood of tofacitinib causing QTcF prolongation appears low. Given the number of occurrences, the clinical evaluator felt this merited inclusion in the RMP as a potential risk.

Gastrointestinal perforations

Gastrointestinal perforations occurred in 12 patients (incidence rate 0.177/100 patient-years): 8 were receiving 10 mg bd dose and 4 were on the 5 mg bd dose (sponsor information from the response to the Delegate's initial Overview, and none occurred in the adalimumab or placebo arms. None was seen in the Phase III studies at the 5 mg dose level, and the 4 cases at 5 mg occurred in the LTE studies (incidence rate 0.12/100 patient-years). In the P2P3LTE, there are also several cases of upper gastrointestinal erosions and ulceration which may lead to perforation. Gastrointestinal symptoms including abdominal pain were common TEAEs reported for tofacitinib.

Comment: Gastrointestinal perforation is a well-recognised risk of patients with RA, especially with the use of NSAIDs and corticosteroids, and while all patients in the 10 mg bd arm affected were using either or both of these medications, the sponsor has not provided this information for the 4 patients on the lower dose. It is unclear as to whether the JAK inhibition of tofacitinib is involved in increasing this risk further. The EMA report identified that this risk profile was consistent with biological agents such as etanercept and tocilizumab, and the sponsor has indicated a higher rate with tocilizumab is reported in the Australian PI.

Laboratory marker abnormalities

Liver function: Liver function test abnormalities were consistently reported in those on tofacitinib across all the pivotal trials, especially those of longer duration, and were

predominantly a mild increase in AST/ALT. These abnormalities appeared to increase with increasing dose of tofacitinib and concomitant MTX/DMARDs.

In the Phase III studies, cases of hepatic enzymes increases were commonly reported. In background DMARD studies, the numbers in the first 3 months were 28 ALT increased and 20 AST increased with tofacitinib, 1 in the adalimumab group, and 11 with placebo.

Liver function related AEs were higher in the tofacitinib 5 mg and 10 mg dose groups (1.8% and 2.5%, respectively) compared with the placebo group (0.5%) and the adalimumab group (1.5%) from 3 to 6 months. After 6 months of treatment, more patients had hepatic AEs in the tofacitinib 5 mg and the 10 mg dose groups (2.4% and 3.3%, respectively) than in the adalimumab group (0.5%). Thus, the potential hepatic toxicity of tofacitinib appears to be greater than for adalimumab, including the rates of severe liver enzyme abnormalities (> 3 x ULN).

In the long term extension studies, 5.1% (163/3227) of patients developed abnormal LFTs, with 0.3% being SAEs and were responsible for 0.7% of all discontinuations. The abnormalities were classified as rises in: ALT (54), AST (40), gamma glutamyl transferase (GGT; 22), 'hepatic enzyme increased' (28), and bilirubin (1). One case met the criteria for Hy's law although the sponsor has responded that this might not necessarily be a case of drug-induced liver injury (DILI) attributable to tofacitinib, as the patient is reported to have responded to azathioprine and corticosteroids under the care of a hepatologist. However, even a single case of DILI is of significant concern, and the possibility of tofacitinib having a causative role is not excluded.

Creatinine rise: In the pivotal studies, those receiving tofacitinib had increases in serum creatinine and a decrease in creatinine clearance although the significance of this is uncertain. In Study A3921064, more cases of acute renal failure were seen in the tofacitinib treatment arms (10) than in the placebo or adalimumab arms (2). The EMA reported much higher absolute numbers who developed acute renal failure in those receiving tofacitinib (19 patients for 5 mg; 22 patients for 10 mg), compared with placebo (2 patients) in the Phase III/long term extension studies. In Study A3921069, rising creatinine levels were the reason for early discontinuation in 3 subjects (2 on 5 mg, 1 on 10 mg), with one abnormality still present (5 mg dose).

The sponsor conducted Study A3921152 (Phase I glomerular filtration rate study) specifically to investigate the effect of tofacitinib on renal function but the study will not be available until the end of December 2013. Thus, this remains an unexplained finding and one that is of concern given the number of patients affected and that it led to discontinuation of the drug in five patients (none in MTX group) in the most recent pivotal trial (A3921069).

Creatine phosphokinase: This was not measured in the Phase II trials but elevated levels occurring in a dose-dependent fashion were observed in the Phase III tofacitinib groups (70 IU/L at baseline to 129 IU/L at 12 months. The percentage of AEs for the 5 mg and 10 mg doses were 0.7% and 2.1% respectively compared with 0.4% and 0.5% for the placebo and adalimumab groups respectively. The placebo group will contain patients on tofacitinib from 3 months and all will be taking tofacitinib from 6 months.

Nine patients in the Phase III studies and 10 in the LTE studies were coded as having rhabdomyolysis/myopathy (creatine kinase 5 x ULN) but without AE associated. This was a reason for discontinuation for 2 patients in Study A3921069, including a patient in their 20s on 5 mg tofacitinib (no information about resolution or severity is recorded).

Haematological

Erythropenia was reported in the 5 mg dose was 3% and 10 mg dose was 1.2% equating to 1.6 and 2.41 new events/100 patient-years, respectively. Three cases were severe in 5 mg group and necessitated discontinuation. Neutropenia rates were higher in 5 mg

group and appeared likely to be a cumulative effect with 0.13 new events/100 patient-years.

In the Phase III studies, one of the five patients with a life threatening decrease in haemoglobin was on the 5 mg dose. In the LTE, mild to moderate haemoglobin decreases of 12.4% and 8.2%, and moderate to severe decreases were reported in 2.8% and 1.1% of the 5 and 10 mg groups, respectively. In this cohort, there were 23 patients with life-threatening haemoglobin decreases.

Comment: this raises the question as to whether the anaemia is mediated by the inhibition of JAK2 kinase activity by tofacitinib. Cases resembling Wernicke's encephalopathy led to the discontinuation of the development program for the JAK2 kinase inhibitor fedratinib, and cases of progressive multifocal leucoencephalopathy (PML) have been reported with ruxolitinib. Given these AEs, the sponsor is requested to provide an updated search to determine whether similar cases resembling Wernicke's encephalopathy, PML, or other demyelinating disorders have been identified.

The sponsor investigated lymphocyte levels in Study A3921073, with 29 patients taking 10 mg bd or placebo for 4 weeks. While memory B cell levels dropped from Day 1 and recovered within 1 day of discontinuation, the CD4+ T cells increased before dropping to below baseline 24 h after ceasing treatment. NK cell counts decreased by Day 28 and took longest to recover (Day 35). In the Phase II trials, no measurement of lymphocyte subsets was undertaken. In the Phase III trials, mild lymphopenia was observed in the 5 and 10 mg groups (24.1% and 25.6% respectively) and an even higher rate of moderate to severe lymphopenia was reported in the 5 and 10 mg groups in the long term studies (58.6% and 31.1%, respectively). Leucopenia occurred in 4.1% of 5 mg group equating to 0.54/100 patient-years. One case was severe and led to discontinuation. The risk of severe infections is very high, and, ten patients developed life-threatening infections. Such patients are also highly vulnerable to opportunistic infections and viral infections.

Comment: The progressive decline of lymphocytes and the relatively slow recovery of NK cells after just 28 days of treatment raise concerns about the reversibility with longer term treatment especially in the context of discontinuation in response to infection. The preclinical study in rats revealed delayed recovery after 6 weeks' treatment with tofacitinib. This NK cell decline persisted with duration of treatment with tofacitinib, unlike adalimumab where the initial increase in lymphocyte counts persisted through the 12 months of that study. Furthermore, the rate of moderate to severe lymphopenia (58.6% and 31.1% in the 5 and the 10 mg dose groups, respectively) in long term extension studies raises concerns about the long term effects on the immune system, and the recovery rate when stopping and risk of infection. The sponsor reports 0.31% patients in this long term safety group receiving 5 or 10 mg of tofacitinib had confirmed absolute lymphocyte counts < 0.5×10^9 cells/L.

Pregnancy

The evidence for teratogenicity and embryonic lethality in two animal models, presented by the nonclinical evaluator, lead to a recommendation that tofacitinib be placed in Pregnancy Category D.

There are no controlled trials of outcomes in pregnant women taking tofacitinib, and the report of outcomes in pregnant women taking tofacitinib in the development phase contains information regarding the safe outcome for only 4 of 13 pregnancies. Of the remaining 9 pregnancies, there were 3 spontaneous abortions (no information provided about cause, stage of pregnancy, any fetal anomalies), 2 were electively terminated with 4 ongoing and with one lost to follow-up. Of additional concern, is that two pregnancies were unplanned and attributed by the investigators to oral contraceptive failure possibly due to a drug interaction with tofacitinib. One woman subsequently had a missed abortion. The 3 spontaneous abortions and two oral contraceptive failures are all serious AEs.

Thus, there remains significant uncertainty regarding whether tofacitinib is safe in pregnancy. It is currently stated in the draft PI that tofacitinib should not be commenced in women who intend to become or are pregnant, nor in those who are breastfeeding.

Lactation

It is excreted in milk in animal models and should not be used by women who are breastfeeding (stated in the PI).

Drug interactions

There is significant potential for drug interactions, specifically those inducing or inhibiting CYP3A4, with ketoconazole doubling the AUC by 103%, rifamipicin decreasing it, and fluconazole affecting both renal excretion and hepatic metabolism. Taken together with the increased toxicity seen with relatively minor increases (such as from the 5 mg to 10 mg dose), and relatively narrow therapeutic window (deaths were observed in monkeys when AUC was 3 times the therapeutic level), concomitant medications need to be monitored carefully.

In the LTE studies, two failures of the oral contraceptive, resulting in unplanned pregnancies were considered possibly attributable to a drug interaction with tofacitinib.

Areas of uncertain risk

In November 2013, the JAK2 kinase inhibitor, fedratinib, was withdrawn from marketing due to the occurrence of several cases resembling Wernicke's encephalopathy during the clinical trials. Progressive multifocal leuokoencephalopathy has been reported in patients taking the approved JAK2 kinase inhibitor, ruxolitinib. As tofacitinib exerts some JAK2 kinase inhibition, the sponsor is requested to perform a search using MedRA terms that would identify if any such cases have been reported in those taking or who have recently stopped tofacitinib, and present this in the response to this Overview.

Clinical evaluator's recommendation

Following the Fourth Round evaluation the clinical evaluator was unable to recommend approval of the submission with the indication as proposed:

> *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. XELJANZ can be used alone or in combination with non-biological DMARDS, including methotrexate. Therapy with XELJANZ should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

The proposed indication does not reflect the status of tofacitinib as a third line agent.

The clinical evaluator would be able to recommend approval of the submission with the following amended indication:

> *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 Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

Risk management plan

The TGA OPR has accepted the EU-RMP Version 1.2 dated 07 June 2013 [Data lock point 29 September 2011] with ASA and has recommended further changes as outlined in their report (see *Pharmacovigilance findings*, above).

It is considered that the sponsor's response to the TGA request for further information have adequately addressed all of the issues identified in the RMP evaluation report, with the exception of some outstanding issues (see below).

The opinion of the ASCOM was sought on 13 September 2013 and noted that in many of the studies, tofacitinib was not being used in the line of therapy proposed in the indication, and therefore the proposed studies will not detect if there are any risks which are specific to tofacitinib when used in that line.

There is no current advice in the draft PI about washout periods for the preceding bDMARD prior to commencing tofacitinib, nor that needed for tofacitinib if proceeding on to a biological therapy.

A number of recommendations for the RMP have been provided by the RMP evaluator and the sponsor should address these matters in the response to this Overview and follow up where appropriate with the OPR:

- The Delegate is of the opinion that there is insufficient characterisation of the risk-benefit profile currently to permit identification of an indication for registration of tofacitinib. The Delegate is in agreement with the OPR and clinical evaluator's comments that *'risks could also be investigated in further comparative studies with bDMARDs. Pharmacovigilance activities may take many years longer to identify risks than randomised controlled trials (RCTs)'*. Performance of such studies comparing tofacitinib with bDMARDs could further characterise the safety profile of tofacitinib, and the sponsor is encouraged to submit the study protocols to the TGA for evaluation prior to the commencement of such studies.
- Implement EU-RMP Version 1.2 dated 07 June 2013 [Data lock point 19 April 2012] with ASA and any future updates negotiated with the OPR as a condition of registration. (see *Conditions of Registration* below)

Risk-benefit analysis

Delegate's considerations

Efficacy

The fundamental questions are:

- Has efficacy as monotherapy been demonstrated? If so, is this demonstrated for the proposed second line indication?
- Has efficacy in combination with other DMARDs including MTX been demonstrated? If so, has this been demonstrated for the proposed second line indication?
- whether the efficacy of tofacitinib 5 mg bd has been adequately established in the population in which the indication is being sought
- If not, is there a clearly identifiable population where efficacy has been demonstrated?

Has efficacy as monotherapy been demonstrated as second line therapy?

Trials A3921045 and A3921069 aimed to address this.

Trial A3921045 demonstrated at 3 months, an improvement in the signs and symptoms of RA with tofacitinib 5 mg but the results for the HAQ-DI and DAS28-4(ESR) were not satisfactorily established. Trials design issues included the arms having concomitant

DMARDs unevenly balanced in favour of tofacitinib (thus this was also not monotherapy for a significant number of participants) and the imputation of those discontinuing for any reason as non-responders, biasing the efficacy results. This study was not designed to, nor makes any claims regarding structural preservation with tofacitinib monotherapy.

Trial A3921069 was not designed to demonstrate the efficacy of tofacitinib as a second line therapy, as it is a first line trial (as stated by the sponsor in the Round 4 response). Further issues with the trial design are discussed above, but given its lack of relevance to the proposed indication, are not recapped here.

Neither study was designed to demonstrate structural preservation by monotherapy with the 5 mg tofacitinib dose at 12 months and sustained at the 2 year mark, as recommended in the EMA Guidelines, in the proposed second line population.

Thus, improvement in the signs and symptoms with tofacitinib monotherapy in the population sought by the sponsor has been demonstrated, but at 3 months only (but not beyond), and there is no evidence for controlling inflammation and preventing the disabling joint damage that occurs with this disease. Study A3921069 was carried out in a different population from the proposed indication, therefore the assessment of data regarding structural preservation and efficacy from later time points would not address this.

Has efficacy in combination with methotrexate been demonstrated? Has efficacy in combination with tDMARD(s) other than methotrexate been demonstrated?

In Trials A3921032, A3921044, and A3921064, tofacitinib was added in to MTX versus continuing MTX alone, and in Study A3921046, tofacitinib plus tDMARD(s) was compared with tDMARD(s) alone.

In the 6 month Study A3921032, the study population had to have received a prior TNFα inhibitor, but up to 3 or more TNF inhibitors had been used by some patients. Thus, this is immediately a population potentially receiving their up to their fifth or higher line of treatment and not the second line population in whom registration is sought. There was some improvement in the signs and symptoms and quality of life with tofacitinib, but no effect demonstrated on the inflammatory process. The issues identified with the trial design undermine these findings and any statistical and clinical significance. The other trial issues are the choice of single agent MTX as a comparator for patients who have required ≥ 1 bDMARD or a bDMARD/tDMARD, the low dose of MTX permitted (7.5-25 mg), the inflexibility to optimise MTX dosing (see Study A3921069 discussion above). In the opinion of the Delegate, the evidence for efficacy in this trial was weak, and certainly not supportive of tofacitinib as an agent likely to modify the underlying disease process; the prior use of ≥ 4 lines of therapy by some patients is not at all supportive of use in the second line, and makes identifying those who might benefit impossible.

In the 24 month Study A3921044, the line of therapy was unclear, making it uncertain whether this is a population receiving tofacitinib as a second line therapy. It is not clear how many prior lines of treatment have been given, or whether the patients were truly progressing on their first treatment.

Adding tofacitinib to MTX resulted in an improvement in the signs and symptoms (ACR20) compared with the control, but as there was no demonstrable slowing of joint destruction, no statistical significance for measures of the inflammatory process or HAQ-DI improvement could be claimed. Thus, there is no proven reduction in the risk of longer term damage. No comparison was possible beyond 6 months as there was no control arm beyond this point. Other trial design issues include the imputation of all who discontinue as non-responders, significant numbers of missing primary efficacy endpoints and depletion of the placebo arm through the early escape design.

Thus, while there appears to be some effect of tofacitinib after 6 months on improving signs and symptoms, there is no effect demonstrated in halting the progression of joint destruction nor the underlying inflammatory process.

Once again, it is not possible to identify from this very mixed population, both in terms of the numbers of prior therapies and also the disease duration, who might benefit from this modest improvement in symptoms. This trial does not clearly show a benefit as a second line therapy and therefore does not support the proposed indication sought by the sponsor.

Study A3921064: This study demonstrates a significant improvement in the signs and symptoms of RA, quality of life but the very small improvement on the underlying inflammatory process (5% absolute improvement) with tofacitinib in combination with MTX is not compelling.

However, this is once again a varied population ranging from the newly diagnosed to those having had RA for more than 49 years, with a highly variable number of prior therapies likely as a result. The sponsor was requested to provide a break-down of the prior lines of therapies for the patients in this trial.

Bringing together all the evidence for efficacy, there is supportive evidence for efficacy in terms of improving the signs and symptoms when used in combination with MTX, but there has not any compelling evidence for reducing the inflammation or the risk of structural progression.

Modest benefit was demonstrated in reducing the signs and symptoms of RA in Study A3921069 but this is a first line trial and the findings are not pertinent to this application.

In combination with tDMARD(s): In Study A3921046, adding in tofacitinib to one or more tDMARDs resulted in an improvement in the signs and symptoms of RA and a minor improvement in quality of life but due to significant missing data, there is uncertainty as to whether there is a significant improvement in the underlying inflammatory process.

The population is once again heterogeneous, with 10% of patients receiving third line or greater (clarification to be sought from the sponsor), and there were differences in the tDMARD background treatment (one third were on combination DMARDs, two thirds on single tDMARD. These findings do not support the current second line indication being sought. Again it is difficult to establish in which line of therapy/population the efficacy has been clearly established.

While there appeared to be ongoing treatment effect in the long term extension 5 mg group with DMARDs, demonstration of longer term efficacy was confounded by use of prior higher doses before entry. The median duration of treatment was 12 months which may reflect discontinuation due to waning efficacy and/or poor tolerability and/or AEs.

Whether the efficacy of tofacitinib 5 mg bd has been adequately established in the population in which the indication is being sought

There were no studies which recruited specifically the population required to demonstrate efficacy as a second line treatment: after failure of a single bDMARD as the sole line of treatment, or after tDMARD therapy. The pivotal trials all contained heterogeneous populations who had either received no or only brief initial treatment, ≥ 1 tDMARDs with some receiving bDMARDs also. It is not possible to generalise the findings from treatment naïve patients or those who have been heavily pre-treated to this population to support the proposed indication. Furthermore, while there was some benefit of tofacitinib in improving symptoms and signs (at 3 months as monotherapy, up to 6 months as combination with MTX or other tDMARDs), the absence of clearly demonstrated improvement in inflammatory or structural benefits suggests this does not prevent long term damage, which is the aim when commencing second line treatment.

If not, is there a clearly identifiable population where efficacy has been demonstrated?

As subjects within each of the trials had received widely varying numbers of prior therapies, and had variable disease in terms of duration since diagnosis, they represent a very diverse population. Consequently, they are likely to vary in terms of responsiveness to further lines of therapy. While some efficacy in terms of controlling signs and symptoms was demonstrated in combination, more so when in combination with other tDMARDs, the trial design did not permit identification of the sub-group where that benefit occurred. The very limited effect on inflammatory markers, and absence of any significant prevention of structural damage, in patient groups beyond second line, raises concerns this does not prevent long term damage. As there are other DMARDs proven in this regard, and no studies comparing the relative efficacy of tofacitinib, this further complicates identifying clearly the population likely to benefit.

Summary/opinion Thus, in the opinion of the Delegate, the studies have neither adequately characterised nor identified the populations who might benefit from tofacitinib therapy.

Safety

Issues

There remain significant unresolved concerns about the potential complications that may arise with long term use of tofacitinib. The manageability and preventability of some of these risks are uncertain.

Infection/immunosuppression

The risk of infection is higher in tofacitinib compared with adalimumab or the placebo group. Patients developed serious and fatal opportunistic infections, and these were only seen with tofacitinib. Sixteen cases of TB infections were seen with tofacitinib but not the placebo, including disseminated TB. These occurred despite protocol-mandated screening, raising the concern of difficulty in preventing such cases. It also suggests a significant impairment of cell-mediated immunity; and the impact of longer term administration and the degree of reversibility with long term use has not been characterised and remains uncertain. In response to the CHMP's concern, the sponsor proposed to recommend discontinuing treatment where lymphocytes decreased to < 0.5 cells/mL but whether this is likely to reduce the risk is unknown.

The incidence of herpes zoster, particularly in Asian subjects, was high with 6/55 cases serious or multidermatomal/ophthalmic (3 occurred on the 5 mg dose); after pneumonia, this was the second-highest cause of infection-related discontinuations of treatment. The incidence rate in the 5 mg group at the April 2012 cut-off was reported as 4.4/100 patient-years, which is a significant ongoing risk that is neither predictable nor preventable, therefore strategies to prevent this cannot be put in place.

Malignancies

There is a steady increase in the risk of malignancies with increasing exposure, including those cancers increased in immunosuppressed patients, which is of concern. The cumulative mortality was restricted to assessment within 30 days of the last dose for the last updated safety summary, which will not capture those who die of cancer unless it is a very late presentation and/or very aggressive.

Cardiovascular risk

Patients with RA are already at an increased risk of CV disease. The longer term impact of the increased rate of hypertension, renal impairment, elevated cholesterol and lipid levels on CV risk, are uncertain and of concern, and cannot be estimated from the data provided. It is important to note that renal impairment and hypertension, both significant risk

factors for CV disease, are not side effects of bDMARDs such as adalimumab, and so represent an additional risk of tofacitinib when comparing the risk-benefit profile.

Some safety concerns are related to an inadequate characterisation of the effects (such as those identified by the EMA with respect to the mechanisms of action and reversibility in the lymphocyte subsets). The number and nature of the opportunistic infections (particularly disseminated) suggest a long term ongoing risk consistent with the immunosuppressive effect but the degree of reversibility has only been clarified with short term administration of tofacitinib. Another safety concern is the accumulation of toxicities with tofacitinib likely to affect CV risk (hypertension, hypercholesterolaemia and hyperlipidaemia, and the apparent renal impairment).

The longer term data presented does not appear to have an adequate duration of exposure to quantify the risk for:

- developing malignancies, particularly lymphoma (rates increase from 30 months for the TNF inhibitor, adalimumab: see PI for Humira)
- CV disease and cerebrovascular disease
- the impact and reversibility of the immune suppressing effects of tofacitinib, especially the lymphopenia, and NK suppression

Trial design

The flaws in trial design that affected the ability to demonstrate efficacy apply equally to establishing the safety of tofacitinib. Both the LTE and P2P3LTE carry over the issues of trials design and the difficulty of determining the risk for a particular population with use of tofacitinib. It cannot be assumed that the risks for treatment in one group with differing prior number of therapies and disease duration can be generalised to another. Patients who have received extensive immunosuppressive treatment may be more susceptible to the risks of tofacitinib. The advice of the ASCOM was sought on 13 September 2013 and identified the specific issue of the potential residual immunosuppression from a prior bDMARD therapy: there would be little data to predict the effects in such patients. ACSOM noted that in many of the studies, tofacitinib was not being used in the same line as the proposed indication and therefore those studies will not detect if there are any risks which are specific to tofacitinib usage in that line. ACSOM particularly specified that to be the case for consideration of a third line indication.

From the Phase III studies, it is not possible to identify a population where the safe use of tofacitinib has been clearly demonstrated. This is further compromised by key problems in the design for the longer term studies. The protocol amendment resulting in a critical dose change to 10 mg at the commencement in the long term extension studies from June 2009 meant no new enrolments at the 5 mg dose occurred outside of China (exempted from amendment). To add to the issue of heterogeneity of the populations with respect to the number of prior treatments and disease duration, there are already data to suggest that this population may have a different PK profile for tofacitinib (higher response rates, increased susceptibility to infections such as herpes zoster, Pneumocystis) and the generalisability of the findings in this population are uncertain. Further characterisation of the longer term safety for the 5 mg dose, will be lost as those continuing on from Study A3921069 to the extension studies will all be mandated to commence 10 mg, eliminating any future data collection about the long term safety of the 5 mg dose in this study population(unless enrolled in China).

There have been four safety updates. The constant redefinition of the patients making up the patient safety data cohorts in the extension studies receiving this dose level has meant there is limited and, at times, no continuity between data submissions. Critically, the absence of key data to permit evaluation with the last updated *Safety Summary* has meant

it is not possible to evaluate the update or to draw conclusions about the safe longer term use of tofacitinib.

Risk-benefit equation

There are significant and some unique safety issues with tofacitinib (that is, not seen with bDMARDs) which raise concerns with both short term use and uncertainties about the safety of long term use. The concerns pertain particularly to the risk of serious infections, longer term risks of malignancy and of CV disease. It is unclear that these are preventable and therefore constitute a potentially unmanageable risk with tofacitinib therapy.

While there has been some efficacy demonstrated with tofacitinib alone or in combination with MTX or other DMARDs, this is restricted to improving the signs and symptoms of RA in those with moderate to severe disease. There is no compelling evidence of an effect on inflammation or on structural progression. Use of a new chemical entity demonstrating such limited efficacy as a second line agent, as proposed by the sponsor, is not justifiable, when gaining control over both the underlying inflammatory disease process and preventing joint destruction are the goals of treatment.

Furthermore, this limited efficacy has not been clearly demonstrated to occur in an identifiable population, for example, second line or third line, either as monotherapy or in combination with DMARDs. The heterogeneous populations within each of the pivotal trials in terms of disease duration and prior lines of therapy means it is difficult to demonstrate efficacy or safety in any one particular group. Generalisations across different lines of treatment cannot be made for either safety or for efficacy.

Consequently, this prevents clear identification of in which patients and in which line of treatment the benefits might outweigh the risks.

Proposed action

Due primarily to concerns about the safety profile of tofacitinib and with the uncertainty about whether the limited efficacy seen has been satisfactorily demonstrated in the proposed second line population, either as monotherapy or in combination with tDMARDs including MTX, the Delegate was not in a position to say that tofacitinib should be approved for the indication requested.

Furthermore, due to the considerable issues and uncertainties about safety noted in the development program, with the longer term safety concerns with tofacitinib usage, the Delegate was not able to propose, at this time, an indication where consideration of approval could be given.

Data deficiencies

- No data were provided to accompany the April 2013 LTE 5 mg bd update submitted for Round 4 evaluation.
- The mechanism of action of the rise in creatinine needs to be determined and the results of Study A3921152 have not been available to explain this.
- There needs to be data to demonstrate the safety and efficacy of tofacitinib compared with bDMARDs, in both the second and third line settings.
- Longer term data is needed to clarify the CV risk of the dyslipidaemia, hypertension and elevated creatinine noted in those on tofacitinib.
- Studies including more subjects over 65 years of age need to be conducted to establish risks and benefits in this age group, especially as this is the age group predominantly affected by RA.
- There are no data about tofacitinib in the paediatric population.

Conditions of registration

Should registration be approved the following are proposed as conditions of registration:

- The implementation in Australia of the EU-RMP Version 1.2 dated 07 June 2013 [Data lock point 19 April 2012] with ASA and any future updates as agreed with the TGA.
- The sponsor must provide the draft educational materials and draft materials for the measurement of effectiveness of the educational program to the TGA for approval prior to the launch of the product in Australia; and measuring the effectiveness of physician educational materials/initiatives within one year following the launch of the product.
- The Delegate, ACSOM, OPR evaluator and clinical evaluator are all in accord that the sponsor must conduct comparative studies with bDMARDs to characterise further the safety and efficacy profile of tofacitinib. The study protocols must be provided to the TGA for evaluation prior to the commencement of such studies.
- Submission for evaluation of the CSR for the Phase I study measuring GFR in RA patients (A3921152; currently ongoing). This study aims to provide additional data to further evaluate the mechanism behind the changes in serum creatinine with tofacitinib relative to placebo in patients with active RA. The CSR was expected to be available for submission at the end of December 2013.

Review of the Product Information

The Delegates proposed revisions to the PI are beyond the scope of the AusPAR.

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and to request the committee provide advice on the following specific issues:

1. Has safety has been adequately characterised and demonstrated to support use in the second line as proposed? Are the long term risks, such as for CV disease, infection and malignancy, sufficiently characterised and manageable with long term use?
2. Whether efficacy has been established for use as monotherapy as a second line treatment. If not, is there an identifiable patient group/line of therapy where a favourable risk-benefit for monotherapy has been demonstrated?
3. Whether efficacy has been adequately demonstrated in combination with (a) MTX or (b) other tDMARD(s) as second line treatment? If not, is there an identifiable patient group/line of therapy where a favourable risk-benefit for combination therapy has been demonstrated?
4. Whether the risk-benefit equation favours the second line indication as sought by the sponsor. If not, whether the risk-benefit equation favours consideration of registration for a modified indication.

Questions for the sponsor

In its response to the Delegate's Overview, the Delegate requested the sponsor include consideration of the following:

1. The sponsor is requested to provide the following information (to complete the table shown below) to determine how many lines of prior treatment patients had had in the pivotal studies.

Study	Design and control type	Population Background Rx in study	% Patients using prior tDMARD or bDMARD use at randomisation		
			Lines	Prior tDMARD use(%)	Prior bDMARD use (%)
Study A3921032	Phase III, randomised, double blind, placebo controlled, parallel group study	TNF inhibitor, tDMARD IR MTX	0 lines 1 line 2 lines 3 lines >3 lines		
Study A3921044	Phase III, randomised, double blind, placebo controlled, parallel group study of tofacitinib as add-on to MTX	MTX IR MTX	0 lines 1 line 2 lines 3 lines >3 lines		
Study A3921064	Phase III randomised, double blind, placebo controlled, parallel group study to compare tofacitinib with placebo and adalimumab in subjects on stable MTX dose	MTX IR MTX	0 lines 1 line 2 lines 3 lines >3 lines		
A3921045	Phase III, randomised, 6 month, double blind, placebo controlled, parallel group trial of tofacitinib as monotherapy in subjects with inadequate response to DMARD*	DMARD IR None	0 lines 1 line 2 lines 3 lines >3 lines		
A3921046	Phase III randomised, double blind, placebo controlled, parallel group study of two doses of tofacitinib and concurrent treatment with DMARDs†	DMARD IR DMARD	0 lines 1 line 2 lines 3 lines >3 lines		
A3921069	Phase III randomised, double blind, study of two doses of tofacitinib versus MTX	MTX naive None	0 lines 1 line 2 lines 3 lines >3 lines		

*Subject must have an inadequate response to at least one DMARD (traditional or biologic) due to lack of efficacy or toxicity. No requirement for prior or concomitant treatment with MTX. All DMARDs, traditional and

biological, including MTX were to be discontinued with an adequate washout period prior to study treatment; IR=inadequate responder
†Subject must have been on at ≥1 background tDMARD and remain on that throughout the study

2. The sponsor is requested to provide an updated search using MedDRA terms that would detect any cases that might resemble PML, Wernicke's encephalopathy, Guillain Barre syndrome or demyelinating disorders to determine if the recently identified risks of JAK2 inhibition apply to tofacitinib. The sponsor is requested to include the number of such cases that were considered possible, probable or definitely attributable to tofacitinib by the study investigators.
3. The sponsor is requested to provide a summary of the 2 year safety findings from Study A3921069.

Response from sponsor

The following presents the sponsor's response to the Delegate's Overview dated 30 December 2013.

The following comments were made in response to comments in the Delegate's Overview:

Safety

- Claims that the safety profile of tofacitinib is not sufficiently characterised are unfounded, particularly in comparison to bDMARDs when first approved;
- Tofacitinib does not present unique, unmanageable safety concerns. The type and rates of key safety events are similar to those with bDMARDs which are already well managed by Australian rheumatologists. There is no reason to believe similar AEs with tofacitinib cannot be managed, in accordance with the PI and RMP;
- The rate and causes of death in patients receiving tofacitinib are not notable in comparison to bDMARDs. Across Phase III (P3) studies, adalimumab had the highest mortality. Cumulative rates from the entire RA program revealed no increase in mortality over time and are consistent with published rates and causes of death for bDMARDs;
- Contrary to the inferences in the Delegate's Overview, no statistically significant differences in rates of serious infections (SIs) were found between the tofacitinib, placebo and adalimumab groups and the rates are consistent with approved bDMARDs; statements in the DO concerning serious and fatal opportunistic infections (OIs) and tuberculosis (TB) are misleading given the very large difference in exposure between tofacitinib and placebo;
- The majority of herpes zoster cases were non-serious. All responded to medical treatment. The rate of serious zoster was comparable to traditional (t) and bDMARDs. It is incorrectly stated that a comparison provided was a sponsor-conducted meta-analysis that only included serious cases. This was not a sponsor analysis and included both all and serious zoster cases;
- Claims of a steady increase in malignancies with increasing exposure are incorrect. There is no increase in malignancy over time and the cumulative death rate did not increase for either 30 day or overall mortality, addressing concerns that deaths from delayed presentation of malignancies were not captured.
- It is important to note that the acceptability of tofacitinib's safety profile has been recognised consistently in 4 rounds of clinical assessments with the final stating *"The risks of infection and malignancy appear to be similar to those for bDMARDs"*;
- A review of data to address the Delegate's concerns with certain oncology therapies found tofacitinib is not associated with an increased risk of Wernicke's

encephalopathy, progressive multifocal leukoencephalopathy, Guillain Barre syndrome or demyelinating disorders;

- The comment that the 10 mg bd dose was refused in the Delegate's initial Overview dated 29 August 2013 is incorrect. The sponsor voluntarily withdrew this dose from the application;
- The comprehensive RMP will address key potential and identified risks.

Efficacy

- Criticism the tofacitinib trial population is not relevant to the proposed indication because it included patients who failed > 1 tDMARD and a wide age range and duration of disease is not consistent with the Australian RA population, local treatment practice, national RA guidelines, Pharmaceutical Benefits Scheme (PBS) reimbursement criteria or previous bDMARD approvals. While the sponsor believes the proposed indication clearly reflects the trial population, the sponsor is willing to amend the proposed indication to replace "previous DMARD therapy", with *"one or more previous DMARDs"*, wording consistent with the indication for approved bDMARDs including abatacept, etanercept, certolizumab and tocilizumab;
- It is incorrectly stated on multiple occasions that tofacitinib does not significantly lower inflammatory markers and thus has no effect on the underlying inflammatory process. These comments are entirely without foundation. Tofacitinib robustly and significantly decreases inflammatory markers (ESR and CRP) that are indicators of the underlying inflammatory process;
- Statements that tofacitinib 5 mg bd *"demonstrated no change on the structural progression"* are misleading. Tofacitinib 5 mg bd preserves structure, with efficacy similar to that of golimumab, a bDMARD approved in Australia with a structural claim;
- Claims that the analysis methods used introduce biases in favour of tofacitinib are refuted. The sponsor is not aware of any more stringent alternative data analysis methods that could have been used, and notes that no alternatives were suggested in the Delegate's Overview;
- All 4 clinical assessments agreed that tofacitinib 5 mg bd, either as monotherapy or in combination, resulted in clinically and statistically significant improvements in the clinical features of RA.

Risk-benefit

- Contrary to comments that *"there are significant and some unique safety issues with tofacitinib (that is, not seen with bDMARDs)"*, the safety events of particular concern to the Delegate, as well as other key safety events, have all been observed in RA patients treated with other approved RA therapies, including bDMARDs, and are familiar to, and managed effectively by, Australian rheumatologists;
- The Delegate's claims of "*limited efficacy*" and statement that "*there is no compelling evidence of an effect on inflammation or on structural preservation*" are unfounded;
- Although tDMARDs and bDMARDs have led to significant improvements in patient outcomes, there remains significant unmet medical need that tofacitinib addresses:
  - Many patients do not respond to or tolerate tDMARDs or bDMARDs, and a disease modifying treatment with an alternative mode of action is needed;
  - Tofacitinib provides robust efficacy as monotherapy, unlike bDMARDs which require MTX to optimise efficacy, a drug that is often not tolerated or contraindicated and with which alcohol is prohibited;

- Unlike bDMARDs, immunogenicity-associated loss of clinical response, AEs and treatment discontinuation are not an issue;
- Oral dosing is a major patient benefit that avoids injection site and infusion reactions, treatment delay or refusal by needle-phobic patients and need for self-injection training, seen with injectable bDMARDs. It doesn't require refrigeration and is easier to transport, store and travel with.

The 4 main issues for which the Delegate has sought ACPM advice are addressed below:

1. Safety: The safety profile of tofacitinib is well described and consistent with current RA therapies. Australian healthcare professionals (HCPs) are familiar with and successfully manage these types of AEs.

Australian rheumatologists have adopted aggressive treatment approaches with tDMARDs and bDMARDs to maximise the chance of favourable long term patient outcomes in this systemic, destructive, disabling and life-shortening disease, accepting that AEs, SAEs and deaths are associated with such immunomodulation and with the underlying disease. There are approximately 16,000 RA patients receiving bDMARDs in Australia[54], and likely a far greater number receiving tDMARDs. AEs with these therapies are successfully, routinely managed by Australian HCPs, including cytopaenias, hepatotoxicity, lipid elevations, serious infections and opportunistic infections, malignancies including lymphoma and skin malignancies, autoimmune and lupus-like syndromes, demyelinating diseases, CV events and gastrointestinal perforations.

The sponsor disagrees that tofacitinib presents unique, unmanageable safety concerns. The type and rates of key safety events, including serious infections, opportunistic infections, TB, malignancies, transaminase elevations, lipid increases, CV events and gastrointestinal perforations are similar to those reported with bDMARDs. Since similar safety events are already managed by Australian rheumatologists, there is no reason AEs with tofacitinib cannot be managed, in accordance with the PI and RMP.

The tofacitinib clinical program is the largest, most comprehensive examination of a new RA therapy since the advent of bDMARDs in the late 1990s. It includes 5,671 patients with 12,664 patient-years of experience and more than 1,000 patients treated for > 42 months, across different patient groups, at different doses, with different prior therapies, and as monotherapy or in combination. The safety profile is well defined for a drug at pre-registration stage, with the extent of treatment experience comparing favourably to bDMARDs. Thus, claims by the Delegate that the safety profile is not sufficiently characterised are unfounded, particularly in comparison to bDMARDs when first approved.

The acceptability of the safety profile has been consistently recognised in all 4 rounds of clinical evaluation...First: *"The rates of SAE with tofacitinib did not appear to be greater than for either placebo or adalimumab"*; Second: *"The benefits [sic] of tofacitinib in the proposed usage are unchanged from those identified in [the First Round Assessment of Risks]"*; Third: *"The additional data did not identify any new safety issues"* and Fourth: *"The risks of infection and malignancy appear to be similar to those for bDMARDs"*. The Delegate's initial Overview did not conclude that there are any unique, unmanageable safety concerns with tofacitinib 5 mg bd, and in the absence of new safety data to contradict the earlier assessments, there is no justification for different conclusions about the safety profile of tofacitinib in the current Delegate's Overview.

Deaths: The sponsor disagrees that death rates with tofacitinib are "notable" in comparison to bDMARDs. Across Phase III studies, adalimumab had a higher mortality rate (1.68/100 patient-years) than tofacitinib 5 mg bd (0.78/100 patient-years).

[54] Prospection PBS 10% Population Sample. Australian Government of Department of Human Services. 2013

Cumulative rates from the entire RA program revealed no increase in mortality over time (Table 41) and are consistent with published rates for bDMARDs (range: 0.23 to 2.3 deaths/100 patient-years)[55]. The rate did not increase over time for either 30 day, or overall mortality, addressing concerns in the Delegate's Overview that deaths from delayed presentation of malignancies were not captured.

Table 41: Cumulative mortality rate across data cuts, P2P3LTE Population

	March 2011 N=4789, E=5651 pt-yrs	**September 2011 N=4791, E=6922 pt-yrs**	**April 2012 N=4789, E=8460 pt-yrs**	**April 2013 N=5671, E=12664 pt-yrs**
	Number of Deaths Incidence Rate (95% CI)	Number of Deaths Incidence Rate (95% CI)	Number of Deaths Incidence Rate (95% CI)	Number of Deaths Incidence Rate (95% CI)
Overall Mortality	34 0.60 (0.43, 0.84)	42 0.61 (0.45, 0.82)	45 0.53 (0.40, 0.71)	67 0.53 (0.42, 0.67)
30-Day Mortality*	21 0.37 (0.24, 0.57)	24 0.35 (0.23, 0.52)	25 0.30 (0.20, 0.44)	35 0.28 (0.20, 0.39)

P2P3LTE = Phase2Phase3LongTermExtension; E = exposure; pt-yrs=patient-years *Deaths within 30 days of last tofacitinib dose

The most common causes of death for tofacitinib were malignancies, infections and CV disease, consistent with RA patients in general[56], and for adalimumab (cardiac arrest, lung cancer and bone marrow hypoplasia) and placebo in the program (multi-system organ failure due to pyelonephritis and sepsis).

Serious and opportunistic infections: Incidence rates of serious infections in the Phase III and LTE studies as of April 2013 were provided. Contrary to inferences in the Delegate's Overview, no statistically significant differences in serious infection rates were found between the tofacitinib, placebo and adalimumab groups.

- *Comparison to bDMARDs*. In A3921064, although there were numerically fewer SIs with adalimumab (3/204, 1.7 events/100 patient-years) versus tofacitinib 5 mg bd (7/204, 4.1/100 patient-years), the difference was not significant. The risk ratio (RR) confidence interval was wide and included unity (RR 2.4 (95% CI 0.63, 9.4)) and thus, statements that the rate of serious infections is higher with tofacitinib than adalimumab are not supported by an accepted definition of significance. The rate for adalimumab in this study was not typical and observed rates with tofacitinib 5 mg bd are comparable to those reported with approved bDMARDs such as adalimumab 4.0/100 patient-years (Humira PI), abatacept 2.87/100 patient-years (Orencia PI), certolizumab (4.0-7.0/100 patient-years, Cimzia PI), tocilizumab 4.7/100 patient-years (Actemra PI) and golimumab 3.0/100 patient-years (Simponi PI).
- *Comparison to tDMARDs*. Rates for serious infections were similar between tofacitinib 5 mg bd (1.817; 95% CI 1.006, 3.280) and MTX (1.869; 95% CI 0.778, 4.491) and slightly lower with tofacitinib 10 mg bd (1.229; 95% CI 0.615, 2.457), supporting that

[55] Emery P *et al.* Ann Rheum Dis 2008, 67:1516; Jones G, *et al.* Ann Rheum Dis 2010, 69:88; Bathon, *et al.* N Engl J Med 2000, 343:1586; Emery P *et al.* Arthritis Rheum 2010, 62:674; Fleischmann R *et al.* Ann Rheum Dis 2009, 68:805.; Smolen J, *et al.* Ann Rheum Dis 2009; 68: 797.
[56] Carmona L, *et al.* Ann Rheum Dis 2007; 66: 880; Gonzalez A, Arthritis Rheum 2007; 56: 3583; Singer RB, *et al.* J Insur Med 2003; 35:144.

rates of serious infections are similar between tofacitinib and approved tDMARDs (Study A3921069).

- *Opportunistic infections and tuberculosis*. Opportunistic infections were infrequently reported. In LTE studies, the incidence rates for opportunistic infections (excluding TB) with tofacitinib 5 mg bd were 0.23 (95% CI 0.12, 0.43) per 100 patient-years of exposure. In comparison, a recent peer-reviewed publication from an adalimumab long term extension study revealed an opportunistic infections rate of 0.3 events/100 patient-years[57], further supporting that the safety profile of tofacitinib is similar to approved bDMARDs. The Delegate's statements regarding serious and fatal opportunistic infections (of which there was 1 case with tofacitinib) and TB are misleading given the very large difference in exposure between tofacitinib (12,664 patient-years across both doses) and placebo (203 patient-years) and duration of therapy (tofacitinib >42 months versus placebo 3-6 months). In addition, TB rates with tofacitinib are similar to those reported for bDMARDs. Twelve of the 16 tofacitinib cases were in countries with high endemic TB rates.

Herpes zoster: Herpes zoster is an important risk in RA patients receiving immunomodulators, including tDMARDs, bDMARDs and tofacitinib. The rate of both all (4.27/100 patient-years) and serious (0.07/100 patient-years) zoster was reported to the TGA, with the rate of serious zoster found to be no higher than bDMARDs (adalimumab/infliximab: 0.37/100 patient-years, etanercept: 0.08/100 patient-years) or tDMARDs (0.09/100 patient-years) (data provided in sponsor's response to Delegate's initial Overview). The Delegate incorrectly stated this was a sponsor-conducted meta-analysis that only included serious cases. This was a summarising table that outlined both all and serious zoster in comparison to published rates for approved bDMARDs and tDMARDs, not a meta-analysis. The sponsor takes issue with the statement that the *"inclusion of just serious infections.....dramatically reduces the number of herpes zoster infections that occurred ...and both downplays the significant morbidity and potential complications of this condition and reduces the appearance of the risk".* Rather, the sponsor's comprehensive approach helps clarify and further understand the risks and morbidities of zoster.

The sponsor disagrees that zoster is a risk that is neither predictable nor preventable, noting the majority of cases (49/55) were non-serious and all responded to management with appropriate treatment if needed, demonstrating it is a manageable risk in clinical practice. Australian rheumatologists are experienced in managing zoster in patients receiving bDMARDs and it is noted the TGA has approved a vaccine (Zostavax) for the prevention of herpes zoster in people > 50 years.

Malignancies (including lymphoma) and rates over time: Claims of a steady increase in malignancies with increasing duration of exposure are incorrect. The malignancy rates quoted from the April 2012 data cut are in patients with up to 30-36 months exposure. However, rates from the same data cut in patients with > 36 months exposure (0.488/100 patient-years) which show no increase, were not quoted. Data provided in the sponsor's Response to the Delegate's initial Overview clearly showed no increase over time (March 2011: 1.03/100 patient-years, September 2011: 1.07/100 patient-years, April 2012: 1.02/100 patient-years, April 2013: 1.02/100 patient-years). Furthermore, in pooled data from five Phase III studies, malignancy rates were similar between tofacitinib 5 mg bd and adalimumab, with the Standardised Incidence Ratio (SIR) for all malignancies (excluding non-melanoma skin cancer (NMSC)) being 1.08 (95% CI 0.89, 1.31) compared with the US SEER database, indicating no increase compared with the general population. Lastly, a comprehensive meta-analysis revealed similar malignancy rates for tofacitinib 5 mg bd compared to approved bDMARDs, as acknowledged by the clinical evaluator in the Fourth

[57] Keystone EC *et al.* J Rheumatol 2013; 40: 1487-97

round assessment. While the SIR for lymphoma was elevated compared to the general (non-RA) population, it was consistent with those reported in bDMARDs trials, and likely represents the role of the underlying disease on lymphoma risk. It is known that certain cancers, including lymphoma, occur at higher frequency in patients with RA compared to the general population, regardless of treatment modality.

CV events, blood pressure and creatinine

The CV safety profile of tofacitinib is characterised by increases in lipid parameters without changes in atherogenic ratios, clinically insignificant changes in blood pressure (BP) (no differences compared with adalimumab) and slightly more frequent episodes of hypertension that can be managed with usual anti-hypertensive measures.

Lipids: Comparable elevations in LDL and HDL have been observed with tocilizumab, an approved bDMARD with no available data concerning CV outcomes with long term use (Actemra PI). In development, tofacitinib-induced LDL elevations were reversed by addition of atorvastatin, indicating it can be managed with usual medical care. Rheumatologists are already familiar with the management of tocilizumab dyslipidaemia.

Blood pressure: BP measurements revealed minimal or no change in BP with tofacitinib compared to placebo or adalimumab. Numerical measurements of BP have greater predictive value than hypertension AEs because in patients with pre-existing hypertension it is common to have spontaneous events of 'worsening hypertension'.

Hypertension: The sponsor disagrees with the claim in the DO that hypertension is not a noted side effect of bDMARDs. Hypertension is one of the most commonly occurring adverse drug reaction with adalimumab (Humira PI), tocilizumab (Actemra PI) and abatacept (Orencia PI), and is also reported with infliximab (Remicade PI), certolizumab (Cimzia PI) and golimumab (Simponi PI). Creatinine: The small increases in creatinine seen with tofacitinib had no identifiable clinical sequelae on renal or CV safety and small mean increases from baseline in creatinine compared to placebo were also seen with adalimumab (Study A3921064).

Cardiovascular events: Importantly, there were no increases in CV events with tofacitinib, with fewer events for tofacitinib compared with placebo and adalimumab in the Phase III studies and no increases over time in the LTE studies. Lipids and CV safety will be further assessed in the proposed RMP.

Characterisation of long term risks of malignancies (particularly lymphoma), CV events and impact and reversibility of immune suppression:

Whilst long term studies will provide more data on malignancy and CV disease rates, the comprehensive pre-registration data package containing safety data > 42 months compares favourably to other approved RA therapies at the registration stage and does not indicate any unmanageable safety concerns. Strategies to address potential risks with tofacitinib are included in the comprehensive RMP and include further assessments of (a) potential risks of malignancies and CV events in a large, safety study with an active bDMARD comparator, (b) lymphocyte and lymphocyte subset counts with long term treatment and assessment of reversibility of lymphocyte and lymphocyte subset counts in patients with a decrease in lymphocyte counts, and (c) an ongoing active surveillance program including the US CORRONA registry and the Japanese Post-Marketing Surveillance study.

Relevance of findings in the long term extension study in view of dose changes and interpretation of different datasets: The Delegate has stated in the Overview that the LTE (A3921024) is of limited value due to a potential dose change between the P2P3 and LTE studies, and that the most relevant group is the P2P3LTE 5 mg bd group, who were on 5 mg bd throughout. Whilst the P2P3LTE 5 mg bd group is relevant, the other analyses and data cuts are important when considering the 5 mg bd safety profile.

The sponsor disagrees that it is difficult to assess long term safety of the 5 mg dose because:

- The safety profile of the LTE 5 mg bd dose group over the long term is very consistent with the P2P3LTE 5 mg bd dose group who have only ever been treated with 5 mg bd. This sensitivity assessment reinforces the interpretation of the long term data.
- A large majority of patients on 5 mg bd in the LTE were enrolled from earlier, short P2 studies and in the LTE studies these patients have been treated for a mean of more than 2.7 years. Given the long duration these patients have been on the 5 mg bd dose it is a reasonable assumption that the safety profile observed in this cohort is attributable to this 5 mg dose.
- During the LTE studies, the majority of patients (85%) did not change dose; therefore the effect of any dose changes on safety (and efficacy) assessments is minor as borne out by the consistent safety profile (and sustained efficacy) over time observed in the program (over a 60 month observation period, the incidence rates of SAEs, serious infection events and malignancies did not increase).
- Patients who advanced to tofacitinib 5 mg bd from placebo at month 3 or 6 do not have a different risk profile from those originally randomised to tofacitinib 5 mg bd. Indeed, regulatory authorities often request to group all patients once they have begun active treatment to provide the largest safety database while on treatment.

The sponsor disagrees with the decision to not consider Phase III safety data provided in the April 2013 data cut off for comparative purposes because the data "appear to be old" and because placebo duration was limited to a maximum of 6 months (for ethical reasons). The main safety analysis for A3921044 was at 1 year and was included in the safety summary. Further, it is unreasonable to discount safety findings from the placebo group on the basis that patients crossed to tofacitinib by 6 months. As is usual practice, events while patients were on placebo were assigned to the placebo group and events after advancing to tofacitinib were assigned to that group, thus event rates with placebo are valid for comparative purposes.

The sponsor believes the comprehensive safety analyses conducted across the development program to be the most responsible and transparent method of presenting safety data in a large clinical program. The safety profile is consistent across the data sets (pooled Phase III, LTE, and safety data in patients treated only with tofacitinib 5 mg or 10 mg bd) and a clear and consistent interpretation of the tofacitinib's long term safety can be ascertained with the findings fully relevant to the current application for the 5 mg bd dose.

2 & 3 Efficacy: Monotherapy and in combination with tDMARDs Robust efficacy has been demonstrated, both as monotherapy and in combination with tDMARDs, in the proposed indication

Indication sought, 'line of therapy' terminology and relevance of trial program to proposed indication:

The sponsor is seeking a 'second line' indication according to the accepted meaning of 'second line' in rheumatology, that is, after failure of one or more tDMARDs ('third line' is defined as patients who have also failed one or more bDMARDs), hence rejects the Delegate's concern over the heterogeneity of the study populations and scepticism they reflect a "second line indication".

The Delegate appears to have incorrectly confused line of therapy with number of prior treatments, inferring that because many patients had failed > 1 tDMARD, the tofacitinib program is not representative of the indication sought. The indication does not state that patients must have failed only 1 tDMARD. The program is completely consistent with the second line indication sought, that is, in patients with an *"inadequate response or are*

intolerant to previous DMARD therapy" and is consistent with Australian practice and guidelines[58] and PBS reimbursement criteria[59], which require a patient to have failed at least 2 tDMARDs prior to commencing a bDMARD. Data from the Australian bDMARD registry indicate that patients have trialled an average of 3.9 tDMARDs prior to commencing a bDMARD[60]. It is also consistent with development programmes for bDMARDs approved by TGA; for example, patients in the 2 pivotal Phase III studies for certolizumab had been treated with a mean of 2.2–2.4 tDMARDs (including MTX) across treatment groups[61, 62]. Certolizumab is approved in RA patients with *"an inadequate response or intolerance to previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs)"* reflecting the patient population studied (Cimzia PI).

All 5 pivotal studies (A3921044, 1045, 1046, 1064, 1032) are entirely consistent with the proposed indication in tDMARD-inadequate responders (IRs). Study A3921032 was in anti-TNF-IRs who had active disease despite MTX treatment, and falls within the indicated population. A3921069 in MTX-naive patients provides valuable supportive efficacy and safety data.

The wide disease duration of patients in the Phase III program criticised by the Delegate is in fact a strength of the program since it is representative of the Australian RA population.

Tofacitinib 5 mg bd shows robust efficacy in tDMARD-IRs as monotherapy and in combination:

The sponsor concurs with the Delegate that improvement in signs and symptoms of RA have been demonstrated with tofacitinib as monotherapy and in combination. However, inferences that these improvements are limited, or modest in magnitude, are not in accord with the data and do not take into consideration comparable findings for available bDMARDs.

Tofacitinib 5 mg bd consistently resulted in statistically significant and clinically meaningful improvement in signs and symptoms of RA (ACR20/50/70 responses), physical function (HAQ-DI) and disease activity (DAS28-4(ESR)). Major efficacy measures were higher for tofacitinib 5 mg bd compared to adalimumab (see also Delegate's initial Overview for details), with twice as many patients attaining the stringent ACR70 response outcome with tofacitinib 5 mg bd than adalimumab (20% versus 9% at month 6, $p = 0.0019$). Thus, it is unfounded to claim limited efficacy for tofacitinib when comparative results are in line with, if not higher, than those seen with bDMARDs approved by TGA.

Tofacitinib robustly improves inflammatory markers and the underlying inflammatory process:

The Delegate's Overview repeatedly and incorrectly claims that tofacitinib does not significantly lower inflammatory markers and thus, has no proven effect on the underlying inflammatory process. These statements are entirely without foundation. Clinically and statistically significant reductions in ESR and CRP were observed with tofacitinib 5 mg bd in all treatment settings. These reductions were numerically large (about 80% reduction for CRP within 2 weeks) and highly statistically significant ($p < 0.001$ or $p < 0.0001$) for all tofacitinib comparisons versus control (data provided in sponsor's response to Delegate's initial Overview). The improvements seen with tofacitinib were similar in magnitude to those with adalimumab (A3921064). Thus, there is compelling evidence that tofacitinib

[58] Australian Rheumatology Association <http://www.rheumatology.org.au/downloads/FINAL-BiologicalRecommendations060111_000.pdf>
[59] <http://www.pbs.gov.au/medicine/item/1964J-3447K-3450N-5735W-9455P-9456Q-9457R-9458T-9459W-9460X-9461Y-9462B-9641K>
[60] Staples MP, *et al.* Rheumatol 2011; 50:166-75
[61] Keystone EC *et al.* Arthritis Rheum 2008; 58: 3319-29
[62] Smolen J, *et al.* Ann Rheum Dis 2009; 68: 797-804

significantly improves inflammatory markers (ESR and CRP) and the underlying inflammatory process.

It appears the Delegate has mistaken DAS28-4(ESR) < 2.6 as an inflammatory marker. DAS28-4(ESR) is not an inflammatory marker, but a composite disease activity score calculated from the number of tender joints, number of swollen joints, Patient Global Assessment visual analogue score and ESR level. Tofacitinib 5 mg bd consistently resulted in statistically significant and clinically meaningful reduction in DAS28-4(ESR) across studies. The observed improvements are similar to those seen with approved bDMARDs. The proportion of patients reaching the stringent DAS28-4(ESR) < 2.6 threshold (known as DAS28 remission), was modest across all arms, due to the high level of initial disease activity (90% of patients with a baseline score > 5.1 (threshold for high disease activity)). The proportion of such patients was similar between the 5 mg bd and adalimumab groups (Delegate's initial Overview Table 8 above; A3921064).

Thus, any conclusions that tofacitinib 5 mg bd is not effective or any less effective than approved bDMARDs at improving inflammatory markers (ESR and CRP), the underlying inflammatory process or disease activity (DAS28-4(ESR)), are not supportable.

Tofacitinib has been shown to preserve structure:

Statements that tofacitinib 5 mg bd *"demonstrated no change on the structural progression"* and showed no *"prevention of structural damage"* are incorrect. Placebo patients demonstrated 4 times as much radiographic progression at 6 months (mean change (Δ) mTSS 0.47 units) versus tofacitinib 5 mg bd (Δ mTSS 0.12 units) (A3921044). The structure preserving effect of the 10 mg bd dose was even greater (Δ mTSS 0.06 units, p = 0.0376 versus placebo). While the 5 mg bd dose group narrowly failed to achieve statistical significance in this study (p = 0.0792), this was an artefact of the less than expected progression in the placebo arm, rather than a lack of effect of the drug. The 5 mg bd dose also continued to inhibit progression through 2 years.

Furthermore, a statistically significantly higher proportion of 5 mg bd patients had no radiographic progression compared to placebo (A3921044) and sensitivity analyses showed statistically significantly less progression versus placebo in poor prognostic factor groups (for example, anti-CCP+, seropositive with a baseline Erosion Score ≥ 3, baseline mTSS > median). There were also significant differences in Δ mTSS between tofacitinib 5 mg bd and MTX (a DMARD known to preserve structure) (A3921069). In MTX-naïve patients, this study demonstrates that tofacitinib 5 mg bd preserves structure. It would be biologically implausible for the drug to preserve structure in patients who had not trialled MTX (A3921069), but have no effect on structure in patients who had (A3921044).

Tofacitinib's effect on structure is similar to golimumab, a bDMARD approved by TGA that has shown significant structural benefit in a MTX-naïve population (GO-BEFORE study, analogous to A3921069) but not in MTX-IRs (GO-FORWARD study, analogous to A3921044), due to limited structural progression in all treatment groups in the latter study (Simponi PI). Golimumab has received approval for treatment of RA in tDMARD-IR patients with a structural benefit indication.

The 2003 EMA guidance[63] states certain requirements *"For agents which are claimed to prevent structural joint damage"*. The Delegate misinterprets "full randomisation" to mean use of a control arm for up to 2 years. In today's RA research paradigm, it is not ethical to continue a placebo control group for 2 years. Such a study would be considered harmful to the welfare of patients and would not be approved by Ethics Committees. Further, the sponsor is not seeking a structural benefit claim at this time. Therefore, neither the EMA

[63] CPMP/EWP/556/95 rev 1/Final. *Points to consider on clinical investigation of medicinal products other than NSAIDS for treatment of rheumatoid arthritis*.

guidance, nor whether a structural benefit has been formally demonstrated in the indicated population, should preclude registration for the indication sought.

Data analysis methods used were conservative, accepted and well-established in RA studies:

In the studies of > 6 months (A3921044, 1046, 1064) placebo patients not achieving a 20% improvement in tender and swollen joint counts at 3 months were advanced to tofacitinib for ethical reasons to prevent harm. Thus, criticism of study design features (in the Delegate's Overview) that ensure the welfare of patients is unreasonable. Any patient, regardless of treatment arm, who did not achieve the required improvements at 3 months, was considered a non-responder at 6 months. This treated all arms equally, maintained the randomisation for 6 months and created a stringent, composite endpoint that required both partial success at month 3 and achievement of the outcome measure at 6 months.

Contrary to criticisms of the non-responder imputation (NRI) method for handling patients who discontinue prior to the primary analysis time point, NRI is the most conservative method available and a well-accepted and established technique used in a wide variety of recent RA studies. It is a more stringent analysis method that generally leads to lower reported efficacy outcomes across all treatment arms than less conservative methods such as Last Observation Carried Forward (LOCO) and 'as observed' analyses. NRI requires patients to complete a sufficient course of therapy and meet response criteria to be considered a responder; therefore the impact of NRI for drop-outs is the same across treatment arms. Sensitivity analyses (such as LOCO and observed cases methods) performed supported the conclusions of the primary NRI analyses.

To clarify the Delegate's concerns, missing data (< 15%) for DAS28-4(ESR) < 2.6 was due to some sites being unable to perform a blinded ESR, and < 5% data was missing for ACR20 and HAQ-DI. Excluded patients were evenly distributed among arms, thus, no bias was introduced.

The sponsor thus refutes any claims that the analysis methods introduce biases in favour of tofacitinib.

4. Risk-Benefit: The benefit:risk for tofacitinib 5 mg bd in the proposed DMARD-IR indication is favourable:

The safety profile of tofacitinib 5 mg bd is well defined for a drug at pre-registration stage. Contrary to the comments made in the Delegate's Overview that *"there are significant and some unique safety issues with tofacitinib (ie not seen with bDMARDs)"* key safety events have been observed in RA patients in association with other approved RA therapies, including bDMARDs, and are familiar to, and managed effectively by, Australian rheumatologists. Risks associated with tofacitinib were managed effectively in all studies and can be managed according to the proposed PI and RMP.

The claims made of "limited efficacy" and "no compelling evidence of an effect on inflammation or on structural preservation" (in the Delegate's Overview) are unfounded. Tofacitinib 5 mg bd has consistently resulted in statistically significant and clinically meaningful improvement in signs and symptoms of RA (ACR20/50/70), health related quality of life including physical function (HAQ-DI) and reduction in disease activity (DAS28-4(ESR)). Importantly, tofacitinib significantly reduced inflammatory markers (CRP and ESR), as indicators of the underlying inflammatory process. These improvements are similar to those seen with approved bDMARDs. Structural preservation has been demonstrated in both MTX-naïve and tDMARD-IR patients and is consistent with the structural benefits of bDMARDs, even though the sponsor is not proposing a structural preservation claim at this time.

This efficacy has been demonstrated in a clearly identifiable population, patients who have failed one or more tDMARDs, consistent with Australian RA guidelines and PBS

reimbursement criteria. The development program is highly representative of the indication sought.

There is a strong clinical need for tofacitinib in Australian RA treatment practice. Tofacitinib 5 mg bd provides a new therapeutic option with a unique mechanism of action, oral administration, proven efficacy, including as monotherapy, and an acceptable and manageable safety profile for patients with moderate to severe active RA who have had inadequate response to or are intolerant to previous therapy with one or more tDMARDs. The balance of benefits to risks is favourable, as recognised by regulatory approvals by the US FDA, Swiss Medic, Japanese MHLW and other competent authorities (14 in total).

Response to delegate's specific questions to the sponsor

These were provided as attachments to the response and are not shown in the AusPAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's Overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Xeljanz film coated tablet containing 5 mg of tofacitinib citrate to have an overall positive benefit–risk profile for the indication:

> *Xeljanz is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response to or are intolerant of both prior traditional DMARDs and at least two biological DMARD therapies. Xeljanz can be used alone or in combination with non-biological DMARDS, including methotrexate.*
>
> *Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

In making this recommendation the ACPM:

- Noted that the standard clinical practice is to treat to target aiming for early disease control
- In line with Australian precedent, advised against a Black Box warning on the risks of immunosuppression and malignancy, at this time, but these must be suitably highlighted in the PI and more importantly in the CMI.
- Noted that nonclinical animal studies provided no proof of disease modification
- Noted tofacitinib to be a potent immunosuppressive agent with a broader mode of action and immunosuppressive effect than bDMARDs
- Noted that efficacy in controlling the signs and symptoms had been demonstrated but there was insufficient evidence of an effect on structural progression (mTSS) for the 5 mg dose in combination with methotrexate in the proposed population
- Was of the view that the study program does not reflect current treatment options eg no adequately powered study to compare with a bDMARD
- Expressed concerns over the severity of the infections observed in the clinical development programme, which exceeds those seen with bDMARDs
- Expressed concern over risk of malignancies eg non-melanoma skin cancers and dose-dependent risk of EBV-related lymphoproliferative disorders or lymphoma in the clinical development programme.

- Advised that the risk of malignancies implies screening for skin cancer is appropriate in Australian conditions.
- Noted the increased rate of herpes zoster infections.
- Noted that while the QT study in healthy volunteers did not appear to provide a safety signal, by six months in the clinical trials, there was an increase in the number of patients with an increase in QT interval >60msec from baseline. This should be added to the RMP.
- Expressed concern over the lack of characterisation of the long term safety profile
- Was of the view that there are outstanding safety issues which require rigorous post marketing surveillance, inclusion in the PI and RMP

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- Negotiation of PI and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- required careful wording to reflect concerns expressed above, especially about infection and malignancies risks
- In the *Pharmacokinetics* section: Figure 1 is not useful and has recommendations on the right hand side which differ from the remainder of the PI.
- In the *Clinical trials* section references to the 10 mg bd dosing should be removed. The results of the 10 mg bd dosing have been removed from the tables but this is unclear in the text.
- The section on radiographic response should be revised as it does not accurately reflect the trial data. The statements should include trial details in the PI pertinent to the population in the indication.
- The statement in the *Contraindications* section which comments that Xeljanz should not be used with other bDMARDs (it specifically lists anakinra which is not available in Australia) however, commonly used TNF inhibitors are not listed.
- A statement on severe renal impairment should be added to the *Contraindications* section as these patients were excluded in the clinical trials.
- A statement in the *Precautions* section of the PI and relevant sections of the CMI to reference the potential increase in cholesterol levels and suggesting periodic monitoring.
- Tofacitinib should be withheld if the lymphocyte count drops below <1 x 109/l rather than 0.5 x 10^9/L as currently in the PI, until the counts recover
- In the CMI the following statements are in different areas of the CMI and need to be harmonised

  - Xeljanz must not be used with other medicines that strongly reduce the activity of the body's natural defences (for example, anakinra, azathioprine and cyclosporine).
  - Tell your doctor if you are taking the following medicines used to suppress your immune system, such as azathioprine, tacrolimus, cyclosporin and mycophenolate.

- The list of side effects in the CMI is not considered to convey the serious nature of many of those listed in a way that patients would understand clearly.
- The explanation of the pregnancy category D proposed is not adequately explained in the CMI.
- A statement in the *Contraindications* section of the PI and relevant sections of the CMI against concomitant use with bDMARDs as this was an exclusion in the trials.
- A statement in the *Precautions* section of the PI and relevant sections of the CMI that patients should consider zoster immunisation prior to therapy or avoid immunisations during therapy.
- The terminology for Chronic Kidney Disease stages should be included in the PI when referring to degrees of renal impairment

Specific advice:

1. Has safety has been adequately characterised and demonstrated to support use in the second line as proposed? Are the long term risks, such as for CV disease, infection and malignancy, sufficiently characterised, and manageable with long term use?

The ACPM advised that safety had not been adequately demonstrated and that there remain several significant outstanding safety issues, both with short term and longer term usage of tofacitinib. These include the risk of serious infections, development of malignancies and uncertainty regarding the longer term effect on the immune system eg lymphocyte counts. Given these concerns, the risk-benefit equation does not favour use for the sponsor's proposed second line indication. Registration of tofacitinib would require robust postmarketing surveillance and these risks to be incorporated into the Risk Management Plan and Product Information.

2. Whether efficacy has been established for use as monotherapy as a second line treatment. If not, is there an identifiable patient group/line of therapy where a favourable risk-benefit for monotherapy has been demonstrated?

The ACPM advised that while efficacy in terms of improving the signs and the symptoms of RA had been demonstrated, there was no significant structural benefit demonstrated with the 5 mg tofacitinib dose as monotherapy in the proposed population. However, given there are outstanding concerns about the safety of tofacitinib, and already other agents available with proven efficacy in controlling structural progression, the ACPM considered that the risk-benefit equation is marginal. However, the ACPM advised leaving open the option of monotherapy for those patients who have been heavily pre-treated and it may be safer to allow monotherapy for this last option, rather than enforce combination therapy.

3. Whether efficacy has been adequately demonstrated in combination with a) methotrexate or b) other tDMARD(s) as second line treatment? If not, is there an identifiable patient group/line of therapy where a favourable risk-benefit for combination therapy has been demonstrated?

The ACPM advised that efficacy for tofacitinib in terms of improving the signs and the symptoms of RA in combination with methotrexate or other tDMARDS had been demonstrated; however there was no significant structural benefit demonstrated with the 5 mg tofacitinib dose in combination with methotrexate in the second line population

proposed in the indication. The studies of tofacitinib in combination with other tDMARDs did not include structural preservation as an endpoint.

Given there are outstanding concerns about the safety of tofacitinib, and already other agents available with proven efficacy in controlling structural progression, the ACPM considered that the risk-benefit equation is not favourable for the sponsor's proposed indication for tofacitinib in combination with tDMARDs. The ACPM considered that there may be a favourable risk-benefit equation for those whose disease has not responded to both tDMARDs and bDMARDs (Trial 1032) and who might have fewer treatment options remaining. See modified indication below.

4. Whether the risk-benefit equation favours the second line indication as sought by the sponsor. If not, whether the risk-benefit equation favours consideration of registration for a modified indication.

The ACPM advised that, taking in to account both their concerns about the safety and the limited efficacy demonstrated in the second line population that the risk-benefit equation does not favour the sponsor's proposed indication. However, for those whose disease is progressing after a trial of other therapies including both traditional and bDMARDs and for whom few treatment options remain, the risk-benefit equation may be acceptable.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Post-ACPM considerations

Delegate's proposed regulatory action

Following consideration of the ACPM advice and the sponsor's response to the Delegate's Overview (see above) the Delegate proposed to approve the submission for the following modified indication:

> *Xeljanz, in combination with methotrexate, is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response to, or are intolerant of, both prior traditional DMARDs and at least two biological DMARD therapies. Xeljanz can be used alone where there is intolerance of methotrexate or where continued treatment with methotrexate is inappropriate.*
>
> *Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

The indication is thus revised from that recommended by the ACPM to reflect accurately the population in which there is evidence to support registration. The basis for this is as follows:

a. This comes from a single study, A3921032, within the RA clinical development program, which examined the use of tofacitinib, in combination with MTX (but not with other tDMARDs), after the failure of at least one TNF inhibitor. The other five studies were carried out in populations who were either newly diagnosed and/or MTX-naïve ("first line") or who had received one or more traditional DMARDs ("second line"), with very few having received biological DMARDs.

b. Methotrexate is specified as the only traditional DMARD to be used in combination with tofacitinib as this reflects the trial design of, and consequent evidence from A3921032. Other traditional DMARDs were not permitted, other

than the antimalarials only used by a small percentage. The only study that specifically examined the use of tDMARDs other than MTX (A3921046) was in a much less heavily pre-treated population where only 12% had had a biological DMARD prior to enrolment; of those, less than half had received ≥ 2 biological DMARDs. The magnitude of any efficacy of tofacitinib in this small sub-group cannot be quantified. There are concerns about the ability to extrapolate from the data available for the whole, much less heavily pre-treated A3921046 population to the heavily pre-treated A3921032 population.

c. Tofacitinib was not used as a single agent in this study and therefore, there is no evidence to support its use as monotherapy in this population. The two tofacitinib monotherapy studies included much less heavily pre-treated patient groups: methotrexate-naive patients and newly diagnosed, previously untreated patients where prior bDMARD therapy was an exclusion criterion (Study A3921069); and those from Study A3921045 who had failed prior DMARD therapy, but only 15% had failed a biological DMARD therapy and 5.7% had received > 2 biological DMARDs. Whether there is any tofacitinib efficacy in this small subgroup cannot be determined. The patient groups within these two trials are not considered comparable with those whose disease has not responded adequately to both biological and traditional DMARDs. Thus, there are concerns about the ability to extrapolate from the data available for tofacitinib monotherapy from these two trials.

d. It is acknowledged that methotrexate is not always tolerated nor continued treatment appropriate and therefore, tofacitinib can be used alone in such patients.

e. It is noted that no evidence was submitted for consideration regarding structural benefits of tofacitinib in this population; this, together with the opinion of the clinical evaluator, Delegate and ACPM that no such structural preservation benefit had been demonstrated in the sponsor's proposed population is reflected in both the ACPM's and the Delegate's modified indication.

The Delegate noted the sponsor's offer in the pre-ACPM response[64] to include "one or more previous DMARDs" in the indication. As this does not reflect the population identified by the Delegate in whom there is a potentially favourable risk-benefit equation, inclusion of this is not supported.

The sponsor's proposed indication for use after intolerance of or failure of previous DMARD therapy is not considered to have a favourable risk-benefit equation for the following reasons:

1. There are safety concerns regarding both the nature and the seriousness of the infections, including disseminated opportunistic infections, viral encephalitis observed with tofacitinib use, as expressed by both the Delegate and the ACPM.
2. The uncertainty regarding the effect of long term usage of tofacitinib on the immune system; in particular there is uncertainty about the reversibility and recovery rates of the NK lymphocyte counts.
3. Efficacy has been established in improving signs and symptoms but neither the clinical evaluator, Delegate or ACPM considered that any effect on structural progression had been adequately demonstrated in the sponsor's proposed population. This absence of any proven structural benefits does not adequately reflect the 'treat to target' intention for those with moderate-severe rheumatoid arthritis where control of joint destruction is key. No evidence has been submitted regarding

[64] Also known as the response to the Delegate's Overview.

structural benefits in Study A3921032, and this is reflected in the ACPM's and Delegate's modified indication. This, together with concerns about the safety profile of tofacitinib, does not support registration for the sponsor's proposed indication (after failure of potentially previous DMARD therapy, that is, potentially one DMARD), given also that there are other therapies where such key efficacy benefits in controlling structural progression have been demonstrated, and where the risks are better understood.

4. The inclusion of at least two prior biological DMARD therapies in the indication was to reflect that both the ACPM and the Delegate have significant concerns regarding the safety profile of tofacitinib. It also reflects that there is limited efficacy, with no evidence for any structural preservation benefits with tofacitinib in this population or the population sought by the sponsor. This indication serves to identify a population where few treatment options remain, and for whom the risk-benefit equation for tofacitinib usage may be considered favourable. It was considered by both the ACPM and the Delegate that the risk-benefit equation for tofacitinib usage in a population who had received less treatment (that is, 1 prior biological DMARD) was not favourable.

The Delegate's proposed actions are conditional upon the issues raised by ACPM and those by the Delegate regarding the PI, CMI and RMP are satisfactorily addressed. Details of the Delegate's requested amendments are beyond the scope of the AusPAR.

Proposed conditions of registration

The Delegate proposed to include the following conditions of registration on Xeljanz and invited the sponsor to comments on these proposals.

1. The implementation in Australia of the EU-RMP Version 1.2 dated 07 June 2013 [Data lock point 19 April 2012] with Australian Specific Annex and any future updates as agreed with the TGA.
2. The sponsor must provide the draft educational materials and draft materials for the measurement of effectiveness of the educational program to the TGA for approval prior to the launch of the product in Australia; and measuring the effectiveness of physician educational materials/initiatives within one year following the launch of the product.
3. The sponsor must conduct comparative studies with bDMARDs to characterise further the safety and efficacy profile of tofacitinib.
4. Submission of the Clinical Study Report for the Phase I study measuring glomerular filtration rate (GFR) in rheumatoid arthritis (RA) patients (A3921152) as a Category 1 submission within 3 months of registration.
5. Submission of the 2 year ECG data from Study A3921044 as a Category 1 submission within 3 months of registration.

Sponsor's response to the Delegate's proposed regulatory action

As described in the letter from the Delegate, the indications proposed by the ACPM and the Delegate, do not reflect the indications that were the subject of the sponsor's application nor the scientific body of evidence for tofacitinib in RA. Pfizer therefore disagrees with the assertions that have been made. In particular, the sponsor notes:

- The long term safety profile of tofacitinib is well characterised for a drug at registration stage, with 12,664 patient-years of exposure at April 2013[65]
  - According to risk characterisation power calculations, the available exposure is adequate to exclude an increase of 1.5 times the background rate of serious infections or all malignancies (excluding Non Melanoma Skin Cancer[66] (NMSC))
  - Tofacitinib has demonstrated consistent safety and persistent efficacy through 48 months[67]
- A comprehensive meta-analysis previously provided to TGA by the Sponsor on 15 October 2013 as part of its response to the initial Delegate's Overview of 29 August 2013 (mutual 'stop-clock' from 11 September 2013 to 15 January 2014), revealed no increase in the rate of serious infections or all malignancies (excluding NMSC) compared to current RA therapies. An updated analysis for serious infections confirms the lack of an increase compared to multiple other therapies approved by TGA[68].
- The nature and severity of serious infections are consistent with those seen with other RA therapies[69, 70, 71]
  - Cases of herpes zoster observed with tofacitinib are manageable in clinical practice, with no increase seen in the rate of multidermatomal/ophthalmic zoster. It is important to note that herpes zoster is not unique to tofacitinib and a substantially increased rate has been reported with multiple other RA therapies approved by TGA[72,73,74]
- The rates of all malignancies (excluding NMSC) and specific cancers (lung cancer, breast cancer, lymphoma, and NMSC) as at August 2013 (15,103 patient-years) are representative of those described for the RA population in general and in RA patients treated with biologic DMARDs, with no suggestion that the rate of any type of malignancy is increasing over time[75]
  - While in study A3921024, the rate of NMSC in patients receiving 10 mg bd was higher than in those receiving 5 mg bd, it is important to note that skin cancers have been reported to occur at higher rates in patients receiving other RA therapies approved by TGA[76, 77, 78]. Any potential elevation in risk of skin cancers is already being managed in Australian clinical practice, in line with local guidelines[79] which advise regular skin checks for patients receiving biologic DMARDs.
- The efficacy of tofacitinib is not limited, and has been recognised in a peer-reviewed independent meta-analysis as demonstrating statistically significant improvement in

[65] Safety Summary Document – Tofacitinib (April 2013 data cut off)
[66] Risk Characterisation Assessment – Tofacitinib Clinical Program
[67] Wollenhaupt J, et al. J Rheum 2014; 41:5; doi:10.3899/jrheum.130683 (in press)
[68] Strand V, et al. EULAR Congress, Paris; 11-14 June, 2014: LB-6145 (submitted)
[69] Greenberg JD, et al. Ann Rheum Dis. 2010 February; 69(2): 380–386; doi:10.1136/ard.2008.089276 (submitted with initial Category 1 application May 2012)
[70] Tran NT, et al. Open Access Rheumatology: Research and Reviews 2013:5 21–32; doi: <http://dx.doi.org/10.2147/OARRR.S40526>
[71] Salmon-Ceron DF, et al. Ann Rheum Dis 2011;70(4):616-23; doi:10.1136/ard.2010.137422 (submitted with initial Category 1 application May 2012)
[72] Che H, et al. Joint Bone Spine (2013); doi:10.1016/j.jbspin.2013.07.009
[73] Galloway JB, et al. Ann Rheum Dis 2013;72:229–234. doi:10.1136/annrheumdis-2011-201108
[74] Veetil BMA, et al. Arthritis Care & Research Vol. 65, No. 6, June 2013, pp 854–861; DOI 10.1002/acr.21928
[75] Malignancy Summary Document – Tofacitinib (August 2013 data cut off)
[76] Amari W, et al. Rheumatology 2011;50:1431_1439; doi:10.1093/rheumatology/ker113
[77] Mariette X, et al. Ann Rheum Dis (2011). doi:10.1136/ard.2010.149419
[78] Raaschou P, et al. BMJ 2013;346:f1939 doi: 10.1136/bmj.f1939
[79] Australian Rheumatology Association – Updated Recommendations for the Use of Biological Agents for the Treatment of Rheumatic Diseases

signs symptoms (ACR20/50/70) and statistically significant superiority to adalimumab (ACR50)[80]

- Furthermore, a peer-reviewed independent pooled analysis upon which EULAR guidelines were based, demonstrated that tofacitinib was more efficacious on signs and symptoms and disability and appeared to be more efficacious on structural damage than control treatment[81]
- The primary goal of RA therapy under the treat to target philosophy espoused in current treatment guidelines, is attainment of clinical remission or low disease activity[82], not preservation of structure as asserted in the Delegate's letter dated 7 March 2014
- Nonetheless, structural benefit for tofacitinib has been clearly demonstrated, with maintenance of radiographic response demonstrated for up to 2 years[83], as per data previously offered to the TGA by the sponsor on 15 October 2013 as part of its response to the initial Delegate's Overview of 29 August 2013 (mutual 'stop-clock' from 11 September 2013 to 15 January 2014)

As a result of the sponsor's disagreement with the proposed indication and the requested changes to the PI, it is unable to enter into the label [PI and CMI] negotiations the Delegate was proposing, and requests that the Delegate exercise delegation under the Therapeutic Goods Act 1989 to proceed to a decision under Section 25 of the Act forthwith, so that Pfizer can avail itself of the appeal rights conferred by Section 60.

Initial decision

The TGA reviewed the quality, safety and efficacy data submitted in support of the application to register Xeljanz tablets containing 5 mg tofacitinib for the following indication:

> *the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to previous DMARD therapy. Xeljanz can be used alone or in combination with non-biological DMARDS, including methotrexate. Therapy with Xeljanz should be initiated and monitored by a specialist physician with expertise in the management of rheumatoid arthritis.*[84]

Pursuant to section 25 of the *Therapeutic Goods Act 1989* ("the Act") the Delegate of the Secretary notified the sponsor of the decision **not to register Xeljanz tablets containing 5 mg tofacitinib** for this indication on the grounds that the efficacy and safety of the product have not been satisfactorily established for the purposes for which it is to be used.

The background and summary of the reasons for this decision (as outlined in the Delegate's letter dated 14 May 2014) are as follows:

Background

On 27 April 2012, Pfizer lodged an application with the TGA to register Jaqinus/Xeljanz (tofacitinib) for the following indication:

[80] Kawalec P, et al. Clin Rheumatol (2013) 32:1415–1424; DOI 10.1007/s10067-013-2329-9 (submitted with Sponsor's Response to initial Delegate's Overview - 15 October 2013)
[81] Gaujoux-Viala C, et al. Ann Rheum Dis 2014; 73:510–515. doi:10.1136/annrheumdis-2013-204588
[82] Smolen JS, et al. Ann Rheum Dis 2010; 69:631–637. doi:10.1136/ard.2009.
[83] Study A3921069 2-Year Clinical Study Report
[84] Note that this indication differs from the indication applied for initially as the sponsor modified the proposed indication during the course of the evaluation.

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

The history of the submission is detailed in the Delegate's Overview, dated 30 December 2013, above (see *Overall conclusion and risk/benefit assessment*). The first 'stop-clock' (5 March-16 April2013) was at the request of the TGA following Pfizer's notification to the TGA of its decision to discontinue the development of the tofacitinib transplantation program due to the serious infection rates and post transplantation lymphoproliferative disorders observed within the renal transplantation program. A second 'stop-clock' (15 May to 2 September 2013) was agreed following Pfizer's notification to the TGA of the negative opinion of the CHMP on 25 April 2013, recommending against market authorisation for tofacitinib on the grounds of safety concerns. This 78 day 'stop-clock' was for Pfizer to supply additional data that had become available since the submission to the TGA in April 2012 for evaluation by the TGA, prior to making a decision. These 'stop-clocks' led to a third round evaluation by the clinical evaluator, following which the clinical evaluator no longer supported the proposed indication but recommended the following modified indication:

> *Jaqinus/Xeljanz is indicated for the treatment of moderate to severe rheumatoid arthritis in adults who have had on inadequate response or are intolerant to previous therapy with both biological and non-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.*

Pfizer rejected the modification to the line of therapy recommended following the clinical evaluator's third round evaluation, but did agree to include the following limitation to specialist prescribers. The following indication is that sought for registration now by Pfizer:

> *Xeljanz is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had on inadequate response or are intolerant to previous DMARD therapy. Xeljanz can be used alone or in combination with non-biological DMARDs, including methotrexate.*
>
> *Therapy with Xeljanz should be initiated and monitored by a specialist physician with expertise in the management of rheumatoid arthritis*

On 28 August 2013, Pfizer submitted an ECG data summary requested by the clinical evaluator in the third round report questions for Pfizer. This was five days prior to the deadline for the Delegate's Overview to request advice from the ACPM. Following an assessment of the ECG data summary both the clinical evaluator and the Delegate had concerns about the safety of tofacitinib and withdrew the support for the consideration of registration (see *Delegate's initial Overview* dated 29 August 2013, Third Round clinical evaluator's report (AusPAR Attachment 3) and *Addendum to Delegate's initial Overview* dated 2 September 2013, above).

A third 'stop-clock' (11 September 2013-15 January 2014) was agreed to allow Pfizer to respond to the 22 questions (including 12 pertaining to the ECG data) from the Delegate's initial Overview. In Pfizer's response on 15 October 2013 to the Delegate's initial Overview (29 August 2013), which contained an unfavourable opinion regarding the safety of the 10 mg dose, Pfizer withdrew its application for registration of the 10 mg bd dose, and is now only seeking registration of the 5 mg bd dose.

Following the fourth round of evaluation, the clinical evaluator again recommended rejection of Pfizer's proposed indication, but recommended approval of a modified indication, as follows:

> *Jaqinus/Xeljanz is indicated for the treatment of moderate to severe rheumatoid arthritis in adults who have had on inadequate response or are intolerant to previous therapy with both biological and non-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.*

This modified indication was rejected by Pfizer. In the Delegate's Overview dated 30 December 2013, the Delegate did not recommend registration on the grounds of safety and efficacy not being satisfactorily established for the proposed use.

After considering the advice from the ACPM and Pfizer's response to the Delegate's Overview (pre-ACPM response), the Delegate proposed to approve the submission for the following modified indication:

> *Xeljanz, in combination with methotrexate, is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had on inadequate response to, or are intolerant of, both prior traditional DMARDs and at least two biological DMARD therapies. Xeljanz can be used alone where there is intolerance to methotrexate or where continued treatment with methotrexate is inappropriate.*
>
> *Therapy with Jaqinus/Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

In Pfizer's response of 20 March 2014, Pfizer indicated that the ACPM's and the Delegate's modified indications were not acceptable and consequently, that Pfizer would not enter into any PI negotiations, indicating Pfizer planned to proceed to a Section 60 appeal and requesting the Delegate proceed to a decision "forthwith". Thus, there are 58 PI and 6 CMI changes which have not been addressed and remain an outstanding issue.

Material considered

In coming to the decision, the Delegate considered the following material:

- The sponsor's application for registration dated 27 April 2012
- Correspondence dated 28 February 2013 regarding the discontinuation of tofacitinib development program in transplantation studies
- Final CHMP Assessment Response and the sponsor's document dated 24 February 2013 for ad hoc CHMP meeting Expert Advisory Group Meeting 7 March 2013
- EMA Report: Outcome of the re-exanimation of the initial negative opinion adopted on 25 April 2013
- US label
- Canadian monograph, which the sponsor stated has been approved, and the Summary of the Basis of Decision
- Adverse drug notifications to the TGA as part of clinical trial reporting requirements
- CPMP/EWP/556/95 *Rev 1 Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis* and CPMP/EWP/1776/99. *Points to consider on missing data*

- Australian Rheumatology Association (ARA) "Updated Recommendations for the use of Biological Agents for the Treatment of Rheumatic Diseases" provided by Pfizer in the post-ACPM negotiations 20 March 2014.
- TGA evaluation reports of clinical data dated 10 September 2012, 30 December 2012, 24 August 2013, 2 September 2013, 4 December 2013
- The sponsor's response to the clinical evaluation date 30 November 2012, 19 November 2013, 22 November 2013, 27 August 2013, 2 December 2013, 13 December 2013
- The sponsor's response to questions from the Delegate dated 6 September 2013, 15 October 2013, 27 January 2014
- TGA evaluation of chemistry data and responses to sponsor's comments dated 21 January 2013 and the Module 3 summary prepared for ACPM
- The ratified minutes of the 149th meeting of the PSC of the ACPM on 21 January 2013
- TGA evaluation of nonclinical data dated 24 January 2013, response to sponsor's comments 21 February 2013
- The RMP evaluations: Post-rounds IV-VI, last dated 16 December 2013, with Advisory Committee on Safety of Medicines advice
- The Delegate's request for advice from the ACPM dated 30 December 2003 ('the ACPM overview')
- The sponsor's pre-ACPM response dated 28 January 2014
- The advice received from the ACPM following consideration of the application at their meeting on 13 February 2014
- the sponsor's post-ACPM response dated 20 March 2014 (see *Other matters,* below)

Findings on material questions of fact

1. There were no outstanding issues in relation to quality raised by the pharmaceutical chemistry evaluator.
2. Tofacitinib is a novel agent with broad mechanism of action, exerting a potent immunosuppressive effect via inhibition of JAK1, JAK3 and to a lesser extent, JAK2 or TyK2. Its broad mode of action differs from the bDMARDs currently registered for use in Australia, which target a single pathway.
3. The following is taken from the clinical overview: tofacitinib "was developed as an oral medication to provide efficacy for patients suffering from RA comparable to injectable biologic agents for the treatment of signs and symptoms, reduction in disease activity, attainment of low disease activity states or "DAS defined remission", improvement in physical function and other patient reported outcomes and inhibition of progression of structural damage."
4. No non-inferiority or superiority trials to compare safety and efficacy of tofacitinib with injectable biological agents have been conducted as part of the program.
5. Pfizer supplied the Australian Rheumatology Association (ARA) "Updated Recommendations for the use of Biological Agents for the Treatment of Rheumatic Diseases", which recommend a bDMARD be commenced after at least two prior non-biological DMARD therapies one of which should be methotrexate.
6. Pfizer's proposed indication is for treatment "after previous DMARD therapy" that is, potentially after a single agent.

7. In Australia, there are currently 6 registered bDMARDs which have demonstrated efficacy in controlling the sign and symptoms, as well as inhibiting the progression of structural damage in those with moderate to severe RA.
8. The EMA Guidelines state structural joint preservation should be demonstrated no sooner than 12 months after commencing treatment in an appropriately designed controlled trial (for example, active comparator), with the demonstrable benefit maintained at 24 months.
9. Pfizer submitted six pivotal, Phase III, randomised, double blind, controlled studies in its application to register tofacitinib which allowed assessment of tofacitinib's efficacy (and safety) (see Table 4 above) in patients with moderate to severe active RA: A3921032, A3921044, A3921064, A3921045, A3921046, A3921069.
10. Safety data for the proposed indication were drawn from these six pivotal trials and 2 long term extension studies, A3921024, A3921041 including those from Phase II trials.
11. Following completion of these individual studies, (study duration ranged from 6 months-24 months), patients could enrol in the long term extension study. Prior to June 2009, the study entry dose was set at 5 mg level but increased after to June 2009 (protocol amendment) to be entry at 10 mg bd for all (except those in Chinese studies), regardless of whether satisfactory efficacy was seen with the 5 mg dose in the trial. Beyond this point, the outcomes were followed as part of the long term extension study.
12. Study A3921032: 6 month study, with 399 patients on MTX with prior failure of ≥ 1 bDMARD (34% patients had ≥ 2 bDMARDs) with moderate to severe RA randomised into 4 groups (2:2:1:1) to receive either bd 5 mg or 10 mg tofacitinib plus MTX paired with placebo control groups on MTX switched to bd 5 mg or 10 mg tofacitinib after 3 months. With 5 mg tofacitinib dose level, there was:
    a. significant ACR20 improvement in 17% subjects
    b. small improvement (8 patients compared with 2 in control) in achieving clinical remission (DAS28-4 (ESR))
    c. significant improvement in HAQ-Dl
    d. no randomised controlled data beyond 3 months as control crossed to tofacitinib at 3 months
    e. minimum permitted MTX dose was 7.5 mg compared with the recommended 20-25 mg in ARA recommendations
    f. these patients could continue in the extension study but after June 2009 were mandated to commence tofacitinib 10 mg bd, and there is no follow-up of the specific group beyond 6 months.
13. Study A3921044: 24 month study with 800 patients comparing tofacitinib (5 mg or 10 mg bd) plus MTX with 3-6 months of paired placebo/MTX; advancement to treatment with tofacitinib/MTX occurred for those not an ACR20 responder from 3 months, otherwise all placebo/MTX groups commenced tofacitinib at 6 months:
    a. Randomised controlled data not available after 3 months due to early escape design; all patients were taking tofacitinib from 6 months
    b. 27% more patients experienced a statistically significant improvement in ACR20 with tofacitinib/MTX compared with the placebo MTX arm
    c. mTSS primary endpoint - no statistically significant slowing of joint progression with tofacitinib at any time point with 5 mg dose level

d. the timing of the mTSS assessment and trial design do not conform with the EMA guidelines for assessing structural benefit in RA

e. statistical significance could not be claimed for other primary endpoints (DAS28-4 (ESR), HAQ-Dl) for 5 mg dose level due to lack of mTSS significance (pre-specified step-down procedure in Statistical Analysis Plan)

f. data missing in 5 mg treatment group: 15% DAS28-4 (ESR), 10% in mTSS, 5% HAQ-Dl.

14. Study A3921064: 12 month study with 717 patients already on a stable dose of MTX to compare adding in tofacitinib 5 mg or 10 mg bd compared with paired placebo; a further arm received adalimumab in addition to MTX:

    a. No randomised controlled data after 3 months due to early escape design

    b. not designed as a superiority nor non-inferiority study for tofacitinib versus adalimumab, and the numbers are too small to provide a meaningful comparison of the two agents' safety or efficacy (as done updated safety 20 March 2014)

    c. significant improvement in ACR20 for tofacitinib (51.5%) and adalimumab (47.2%) compared with control (28%)

    d. small but significant improvement in HAQ-Dl, DAS28-4 (ESR)

    e. DAS28-4 (ESR) data missing for 36 subjects in placebo and treatment arm; absolute reported treatment difference between arms was 11 patients.

15. Study A3921045: 6 month study of 3 months tofacitinib versus placebo control before all crossed to tofacitinib:

    a. no randomised controlled data after 3 months

    b. the placebo control arm of no active treatment is not the recognised standard of care

    c. concomitant antimalarials used in 18% tofacitinib compared with 12% control

    d. significant improvement in ACR20 response 59.8% versus 26.7%, % HAQDl but not in DAS28-4(ESR).

16. Study A3921046: 12 month study of tofacitinib in combination with a tDMARD (although prior use of bDMARDs was permitted) compared with paired placebo groups (also on a background DMARD):

    a. tofacitinib resulted in statistically significant improvement in ACR20 (21%), HAQ-Dl and DAS28-4(ESR)(6%) at 6 months

    b. no randomised controlled data after 3 months, all patients were taking tofacitinib from 6 months.

17. Study A3921069: 24 month study of tofacitinib vs MTX in patients with no previous MTX (including 57% newly diagnosed; 43% a prior treatment):

    a. not same population intended for the proposed indication therefore findings do not pertain to the proposed indication

    b. comparator dose range permitted of 10 mg-20 mg MTX was lower than ARA recommendations of 20-25 mg

    c. data missing for 15% of subjects regarding MTX doses

    d. significant improvement reported in structural benefit demonstrated at 6 months, 25% on tofacitinib had ACR70 significantly improved compared with 12% on MTX but this is not the proposed target population.

Safety

1. Pfizer advised the TGA on 28 February, 2013 that the tofacitinib development program in transplantation was discontinued due to concerns about severe infection and post-transplant myoproliferative disease.
2. Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens were reported in patients on tofacitinib. These included BK encephalitis (seen where there is considerable immunosuppression, such as in transplant recipients, HIV infection), disseminated opportunistic infections including TB, cryptococcal meningitis, with some patients not reported to have made a full recovery. Pneumonia was the commonest cause of treatment-related death in the trials and infections (including herpes zoster) were the leading cause of treatment related AEs leading to discontinuation.
3. Adverse reactions reported to the TGA as part of the clinical trial reporting requirement in Australia included cases seen more frequently with immunosuppression: 2 cases with squamous cell carcinomas of the skin (including one with multiple synchronous lesions, one with a 6 cm scalp lesion), basal cell carcinomas, melanoma and a renal cell carcinoma (2 cases since Delegate's overview of 30 December 2013). It is stated in Pfizer's response of 20 March 2014 that the rate of non-melanoma skin cancer may be higher than that for bDMARDs.
4. The updated safety data provided by Pfizer on 20 March 2014 suggests that the rates of serious AEs including infections and malignancies, although non melanoma skin cancers may have increased (no data from April 2012).
5. 5 mg bd Xeljanz was associated with statistically significant 4-7 bpm decreases in heart rate and 4-8 ms increases in the PR interval compared with placebo. Currently the recommended PI changes do not incorporate this, and these would need to be included if tofacitinib were registered in the future. Also cases of interstitial lung disease possibly clustered in Asian subjects were identified and need to be included in any PI changes.
6. A Phase IV study has been commenced <www.clinicaltrials.gov> to address unanswered questions raised about the safety (particularly major adverse CV events, rates of malignancy; also opportunistic infection, hepatic events) of tofacitinib compared with bDMARDs; the estimated end of study date is 2019.
7. There are 64 changes to the PI and CMl recommended by the TGA, including 48 regarding safety that have not been addressed.

Efficacy

8. The proposed indication is for treatment of patients who have moderate to severe RA either who do not tolerate or whose disease does not respond adequately after previous DMARD therapy, that is, potentially a single tDMARD.
9. The studies submitted by Pfizer demonstrate efficacy for limiting the signs and symptoms of RA. However there is no evidence of a statistically significant inhibition of structural joint progression with the tofacitinib 5 mg dose.
10. Where MTX was the comparator or control arm in the tofacitinib Phase III studies, both the maximum dose specified and median dose subsequently used were lower than that the ARA recommendations Pfizer provided on 20 March 2014. This would favour the tofacitinib treatment arm.
11. There were missing data and the method of imputation of such data may lead to bias.

Findings relevant to establishment of both efficacy and safety

12. The clinical trials submitted by Pfizer had significant issues with loss of randomised controlled data due to the early escape design and missing data. A lower dose of MTX was used in the trials than is recommended by the ARA. These issues affect the quality of the studies, and reduce the certainty of the findings obtained.

13. In Pfizer's post-ACPM response, Pfizer states that the inclusion of structural benefits (as stated in my letter of March 7 2014) is not part of the treatment to target approach, citing the ARA recommendations Pfizer supplied in support. The recommendations state (with Delegate's **emphasis**): "The goal for treatment is clinical **and radiological remission** with treatment to target strategies". The number of agents with such proven efficacy registered for this particular indication, and the stated inclusion of structural disease progression in their Australian approved indication argues against Pfizer's position.

14. Pfizer's post-ACPM response: Pfizer claim there has been structural benefit demonstrated and that the TGA refused to accept the data offered (Study A3921069). Although these data were received at a late stage by the TGA, and as such have not been formally evaluated, the Delegate reviewed this material for the purpose of this decision and made the following observations (as also made in the Delegate's Overview/request for advice from ACPM, December 30 2013). This late study report provided by Pfizer was not carried out in the target population identified for the proposed indication, and therefore, the findings cannot be extrapolated and are not pertinent to this application. The study carried out in the relevant target population (A3921044), and submitted by Pfizer with its application, failed to demonstrate any structural benefit.

15. As noted in the Delegate's Overview, the presentation of the safety data utilises several different reporting populations over time. This made it difficult to track safety in any one population over time, and this problem persists in the safety summary provided on 20 March 2014. The data presented comes from at least 3 different populations (who have had differing doses, durations of treatment) which are then further variously divided by dose level. Although described as a separate group, for the P2P3LTE 5 mg bd group (who are most relevant as they have only ever received 5 mg) there is not a separate presentation of the duration/treatment exposure for this population, and there is only the one table with data for this group. Within this table, there are no data from the April 2012 cut-off to compare with the April 2013 cut-off for the rate of non-melanoma skin cancers. Instead this is provided for the 5 and 10 mg doses combined or the total long term population (all dose levels combined). This limits any conclusions that can be drawn for the proposed usage.

Reasons for decision

1. The Delegate did not believe that safety of tofacitinib has been satisfactorily established for the proposed use. The Delegate was concerned by both the nature and the severity of the infections reported with tofacitinib, including BK encephalitis and disseminated opportunistic infections, and these were also concerns of the ACPM. The additional safety data provided by Pfizer on 20 March 2014 focuses on establishing there has been no change in the rate of serious infections, but it is the severity of these infections and the lack of recovery in some reported cases that is of major concern, rather than the rate alone.

2. There remains uncertainty regarding the effect of long term usage of tofacitinib on the immune system; in particular the reversibility and recovery of the NK lymphocyte counts with long term usage have not been demonstrated. Natural killer lymphocytes are known to play a role in host defence against malignancy.

3. The Delegate was concerned about the severity of the skin cancers that occurred in Australian patients on tofacitinib as reported to the TGA. These include cases of squamous cell carcinomas (multiple in one patient, large in another) with a high risk for developing metastases, and melanoma. As with the infections the severity of such cases is the cause for concern, which is not captured by Pfizer's assessment purely of rates of malignancies in Pfizer's 20 March 2014 post-ACPM response. Furthermore, Pfizer did not agree to including these Australian cases in the PI under *Non-melanoma skin cancers* section nor to my request to change the recommendation from "periodic" to "regular" checks to ensure early detection and treatment. The CMI contains no specific information or advice about skin cancer risk and monitoring: this is highly relevant to Australian patients and prescribers, and needs to be addressed should registration be considered in the future.
4. Other cancers reported in Australia and in the updated safety summary are those seen in immunosuppressed patients (for example, renal cell carcinoma).
5. The PI requires extensive revision to be a document supporting the safe use of tofacitinib and to be a correct, factual account of the outcome of the clinical trials: 40/58 changes to PI and 6/6 for the CMI pertain to safety recommended by me and by the ACPM and Pfizer has refused to address these in its post-ACPM response; the remainder include issues such as correction of inaccuracies in describing details and findings of the clinical trials, for example, claims of efficacy generalised from longer duration trials to those of shorter duration, where no such evidence exists.
6. The Canadian monograph (submitted by Pfizer) raises new concerns about heart rate decrease and PR interval prolongation and interstitial lung disease, possibly clustered in Asian subjects (the latter was identified in the periodic safety update report in the pre-ACPM response).
7. While the evidence submitted by Pfizer does indicate some efficacy in respect of improving signs and symptoms, the quality of the clinical trial data undermines the certainty of these findings. Further, the Delegate did not consider that the evidence submitted by Pfizer demonstrates a satisfactory effect on structural progression of the disease in the proposed population. This opinion is supported by the clinical evaluator and the ACPM. It is also reflected in the recently approved indication in Canada "for treatment of 'the signs and symptoms' of rheumatoid arthritis". In the Delegate's view, this indicates that there is no structural benefit approved, and the clinical trial section in the monograph supplied by you does not contain any such claims. In their negative opinion, in addition to the safety concerns, the CHMP state there has been no evidence of any structural benefit.
8. This absence of any proven structural benefit does not adequately reflect the 'treat to target' intention for those with moderate to severe rheumatoid arthritis where control of joint destruction is key. Pfizer's continued claim of proven benefit in reducing structural progression is drawn from a study carried out in a mostly treatment-naive and/or methotrexate-naive population which is not the population in Pfizer's proposed indication. The findings are not pertinent to the proposed usage. Inhibition of structural disease progression, and comparable efficacy with the injectable bDMARDs were stated in the *Clinical Overview* of Pfizer's application as aims of the development program: these have not been achieved.
9. There are 6 bDMARDs currently registered in Australia which are proven to improve the signs and symptoms and inhibit structural disease progression in the target population. The Australian Rheumatology Association recommendations (provided by Pfizer) advise commencing a bDMARD after failure of 2 non-biological DMARDs. Pfizer's proposed indication for tofacitinib, a medicine with significant safety

concerns, and not proven to inhibit structural progression (unlike the bDMARDs), to be used potentially after a single agent does not fit with these recommendations.

10. The Delegate had concerns about the safety profile of tofacitinib, and the limited efficacy does not support registration for the proposed usage and indication (particularly after the failure of potentially only one DMARD), given also that there are other therapies where such key efficacy benefits in controlling structural progression have been demonstrated, and where the risks are better understood. Pfizer's expert witness in the pre-ACPM response identified unmet need as a reason for registering tofacitinib, but for the proposed usage, there are six different options.
11. The wording of the proposed indication does not indicate the limited efficacy demonstrated in the intended population, that is, that inhibition of structural progression has not been demonstrated. The six bDMARDs registered in Australia for the treatment of the intended population contain specific wording that indicates whether or not structural benefit is proven. The Delegate noted that in the monograph Pfizer supplied (16 April 2014), that the wording for the recently approved indication for tofacitinib in Canada, is *"for reducing the signs and symptoms of rheumatoid arthritis"* and no claims of structural benefit are made in the *Clinical Trials* section.

Conclusion

Taking into account the material findings of fact and reasons outlined above the Delegate formed the view that the safety and efficacy of tofacitinib for the purposes for which it is to be used have not been satisfactorily established. As such the Delegate of the Secretary decided not to register tofacitinib on the ARTG.

Other matters

Pfizer's post-ACPM response included 1 safety summary, the Australian Rheumatology Association recommendations (see above), a statement with no authorship, an abstract for a meeting, a report prepared for the "ANSM", a range of journal articles mostly about risks with other agents, and the final CSR for Study A3921069. In correspondence to the sponsor (25 October 2013), and in the Delegate's Overview (30 December, 2013), the Delegate stated that this report would not be accepted for evaluation by the TGA. However, the Delegate reviewed this material for the purposes of the decision and made the following observations: it was conducted in a different population and that the safety and efficacy findings are therefore not pertinent to the proposed use. A safety summary from the study was provided in the pre-ACPM summary which did not reveal any new safety signals. Given that this material was provided late in the evaluation process, this final study report has not been evaluated formally.

The report for the "ANSM" contains several issues of concern, likely to lead to an underestimate of the causality and severity of any immune suppression-related cancers: firstly, non-melanoma skin cancers which are likely to be under-reported in any case (often not excised by the doctor treating RA), are not recorded as SAEs, and secondly the term "squamous cell carcinoma" was reserved for the skin lesions, with other organs being classified according to the primary organ for example, lung cancer. There is ample evidence from transplantation studies that squamous cell carcinoma rates, particularly where virally-mediated, in a range of organs (including lip, oral cavity, vulva, cervical, skin) increase with immunosuppression[85]. These cases and the potential relation to the

[85] Collett, D., Mumford, L. et al "Comparison of the incidence of malignancy in recipients of different types of organs: a UK registry audit" *American journal of Transplantation* 2010;10: 1889-1896.

immunosuppression from tofacitinib are likely to be lost if classified with other cancers arising in the same organ with different histology.

The references include several about the toxicities of the bDMARDs. As clinical trials are conducted under very specific circumstances, it is not possible to compare the AEs rates with the rates in the clinical trials of another drug. The inclusion of a US study of skin cancer rates with bDMARDs is not relevant when Australia has the highest rates of skin cancers in the world. The Delegate noted the sponsor's planned study on <www.clinicaltrials.gov> which aims to address these outstanding issues, with an anticipated closure date of 2019.

While the Delegate has not relied on this material for the purposes of decision-making, the Delegate drew the sponsor's attention to the clinical algorithm in the US evidence-based website, Up To Date (last accessed 12 May 2014) which incorporates tofacitinib, as it is registered in the US contains information. It only recommends tofacitinib be tried in those with moderate to severe rheumatoid arthritis after failure of the following treatments tried in consecutive order: a tDMARD, combination with another tDMARD, 2 TNFα inhibitors each tried with MTX; if still no response then abatacept, tocilizumab or rituximab. Consideration is only given to tofacitinib at this point (that is, after ≥ 5 other treatment agents), but heavily qualified as follows, *"the relative role of tofacitinib in patients who have had an inadequate response to other DMARDs is unclear. A potential advantage of this medication is that it is administered orally, but data regarding the AEs and outcomes with this drug compared with other antirheumatic medications are more limited compared with what is known regarding other available agents."*

The sponsor provided late in the submission (post-ACPM) references in support of the efficacy of tofacitinib. While the following has not been relied upon in making the decision, the Delegate draws the sponsor's attention to literature which may be taken into account should the sponsor wish to seek an internal review. This includes the following independent systematic review and meta-analysis of the efficacy and safety of tofacitinib for the proposed usage, where the quality of the evidence was described as being "exceedingly low; long term large-scale, and high quality post-marketing research is suggested to further verify the conclusion[86]".

Review of initial decision

Following the initial decision described above, the sponsor (under cover of correspondence dated 11 August 2014) sought a review of the decision under the provisions of Section 60 of the Act. This was accompanied by expert opinion from three senior Australian rheumatologists and an updated PSUR dated 2 July 2014. The applicant also proposed a newly worded indication as part of the appeal:

> *Xeljanz is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. Xeljanz con be used alone or in combination with non-biological DMARDs, including methotrexate.*
>
> *Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of the rheumatoid arthritis.'*

[86] Zhang, X., Liang, F., et al "Tofacitinib for acute rheumatoid arthritis patients who have had an inadequate response to disease-modifying antirheumatic drug (DMARD): a systematic review and meta-analysis: *Clinical Rheumatology* 201433 (2): 165-173.

Grounds of the appeal

The grounds of the appeal were set out under two headings: deficiencies in the decision making process and deficiencies in the scientific evaluation.

The grounds, as described by the Delegate of the Minister, are set out and discussed below.

Deficiencies in the decision-making process

Inconsistencies and contrasting findings during the evaluation process.

The applicant expresses concern that there has been 'evidence of inconsistencies, misinterpretations and contrasting findings in the evaluation process.'

The TGA has four primary evaluation areas whose work is provided to a Delegate for an overarching assessment of an application. A Delegate is not obliged to accept the views of an evaluator but is obliged to assess the adequacy of the evidence independently. The Delegate may also consult with experts in an advisory committee. Inevitably there will be differences in interpretation and conclusions arising from such a system and these most often reflect a robustness of review of the scientific evidence.

Failure of the delegate to follow the recommendation of the ACPM

The applicant expresses concern that the Delegate in the letter of 7 March 2014 proposed a modified indication to that recommended by ACPM.

ACPM is an advisory committee not a decision-making committee. Delegates are obliged to reach their own decision on each application and it would not be a precedent for a delegate to reach a different conclusion to the advisory committee.

The applicant also expresses concern that 'no new scientific evidence was put before the Delegate to lead to a change of mind between the proposal to approve the application and the subsequent decision.' The applicant notes that a decision may be made under Section 25 without a PI and CMI as section 25AA is a separate statutory step. The applicant also noted that the issues of heart rate decrease and PR prolongation and interstitial lung disease had been raised either during the evaluation or in the pre ACPM safety update and to its mind had been resolved. The applicant queries the appropriateness of the Delegate raising these at reason 6 for the decision to reject.

Denial of procedural fairness

The applicant is concerned that in the decision letter the Delegate recorded the existence of a clinical algorithm in the US web site Up to Date and two published papers. The applicant notes none of these sources of information had been brought to its attention previously and is concerned at the possibility of selective quoting of negative references and the impact on the decision. The Delegate indicated no reliance on this material for decision making purposes. As the Up to Date material is to of a kind that is not normally considered evaluable for regulatory purposes the Delegate of the Minister has not considered it further here. The two articles have been reviewed for completeness. One is a meta-analysis relying on published literature early during a product's life cycle with the consequent difficulties of lack of published evidence compared to the extent of material contained within the submitted dossier. Nevertheless the article has a positive conclusion concerning the efficacy of tofacitinib. The other is a general article describing the increase in incidence of cancer in organ recipients in the UK with the only potential relevance to the consideration of tofacitinib in rheumatoid arthritis being description of a general recognised effect on tumour incidence associated with immunosuppression, not being specific to tofacitinib. Neither was considered further in the Delegate of the Ministers letter.

Encouragement to submit "new information" under Section 60A

The applicants concern at the reference to two published papers is set out in terms of implications if they should have been required to submit 'new information' and in terms of the Delegate of the Secretary directing the consideration of the Delegate of the Minister. These concern are noted and the applicant is reassured that the Delegate of the Minister is not regarding these papers as "new information" and as discussed above is not considering them further here.

Delegate's comparison of tofacitinib with the bDMARDs

The applicant refers to section 25(1)(d) of the Act and the requirement for an application to be assessed for whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established.

The applicant notes the Delegates comment that [the] 'concerns about the safety profile and the limited efficacy does not support registration for the proposed usage….given that there are other therapies where such key efficacy benefits in controlling structural progression have been demonstrated, and where the risks are better understood.'

Inadequate application of scientific principles

The applicant contends that the Delegate has 'not consistently applied established scientific principles to the clinical safety evaluation of tofacitinib and has disregarded data generated according to internationally accepted methodology for Risk identification, Risk Assessment, and Risk Minimisation' and that this has affected the conclusion that the safety of tofacitinib has not been satisfactorily established for the proposed use.

Relevant information excluded from the evaluation

The applicant expresses concern that the Delegate appeared to have focused on the 5 mg group for safety analysis when consistent with usual regulatory practices all dose levels would be considered. The Delegate of the Minister agreed that this is consistent with usual regulatory practice although some emphasis may be given to the intended dose in the proposed use.

Errors in systematic interpretation of safety information

The applicant expresses concerns that the TGA has not consistently followed standard systematic principles for interpretation of safety data. The applicant acknowledges that objective measures will not be available for all parameters but contends that they should be used where available to investigate potential safety signals. Examples discussed are severity of infection (where the applicant contends there is no objective evidence to support the view that the there is a greater severity of infections with tofacitinib) and malignancy (where the applicant argues that with a high background rate for non-melanoma skin cancer in Australia causality based on reporting of events is complex and claims that severity is greater with tofacitinib are subjective and based on selective sampling).

Deficiencies in the scientific evaluation

Safety

Adequacy of the tofacitinib safety database

The applicant contends that the size and scope of the tofacitinib safety database are sufficient to allow a determination of 'fit for purpose' under the Act, noting that 5671 patients had received at least one dose of tofacitinib in the RA trials submitted to TGA, over 2000 RA patients have been treated for over 3 years and over 1000 for 4 years or longer with approximately 5518 patient-years of exposure to tofacitinib in RA post marketing experience. A copy of the PSUR dated 2 July 2014 accompanied the appeal.

As noted by the applicant this extent of exposure equals or exceeds that available at the time or approval for some bDMARDS.

Infections

The applicant refers to reason 1 of the Delegate's decision letter, noting that use of tofacitinib, as with other approved immunomodulatory therapy, is associated with risks arising from this mechanism of action, including the occurrence of serious and other important infections.

Looking at serious infections as any infection that resulted in death, was life threatening, required impatient hospitalisation or prolongation of hospitalisation, resulted in persistent or significant disability/incapacity, resulted in a congenital abnormality/birth defect or required treatment with a parenteral antimicrobial the applicant calculated the incidence rate for serious infection across the studies at around 3 percent. The rate was consistent across studies and over time and comparable with the reported rates seen for bDMARDs.

The applicant notes that opportunistic infections, that may occur in those who are immunocompromised or on immunomodulatory therapy, are rare and incidence rates are difficult to directly compare. However it is recognised that TNF inhibitor (TNFi) agents are associated with increased risk of bacterial, fungal and viral opportunistic infections. Tuberculosis is the most common opportunistic infection seen with immunomodulatory RA treatments including tofacitinib where overall it occurred at an incident rate of around 0.21. Data form the applicant demonstrated that rates of TB seen in tofacitinib trials varied by region and reflected the underlying incidence of TB in the trial communities which included countries with high endemic rates of TB. Rates of TB and extent of extra pulmonary involvement were broadly similar to those seen with other biological agents. There were not deaths from TB in RA trials of tofacitinib.

Other opportunistic infections occurred at an incident rate of around 0.25 and included oesophageal candidiasis, CMV, cryptococcosis, pneumocystis pneumonia, multidermal herpes zoster, non-tuberculosis mycobacteria and BK encephalitis. The latter has not been reported in RA patients on TNFi agents but there was a single tofacitinib case diagnosed by PCR in a patient with septic arthritis who recovered. The rest have all been reported in RA patients. There was one pneumocystis death and the other patients were reported as recovered or recovering.

NK Lymphocytes and malignancies

The applicant refers to the Delegate's comment on long term safety and the uncertainty of long term effect on NK lymphocytes. The applicant notes that information on recovery of NK lymphocytes, amongst others, to baseline levels on long term therapy to 22 months was submitted in June 2013.

The applicant notes that the incidence rate for malignancy excluding non-melanoma skin cancer (NMSC), while lower in the first six months as expected, remained consistent over time thereafter. The standardised incident ratio (SIR) for all malignancies excluding NMSC as compared with the US Surveillance Epidemiology and End Results database is 1.08 (95% CI: 0.89, 1.31) indicating the overall rate is similar to that of the US population.

The applicant notes that the rate of NMSC for the 5 mg dose is similar to that reported in the literature for bDMARDS but acknowledges the rate is higher for the 10 mg dose, which has been withdrawn. The applicant has also corrected the report of the 6 cm x 14 mm SCC skin cancer to confirm it was 6 mm x 14 mm. NMSC were seen in 0.79% of patients to 19 April 2012 with an overall incidence rate of 0.451 per 100 patient-years. The applicant indicates it has classified this as an identified risk and agreed to amend the RMP and PI to reflect this. The applicant recognises that particularly in the Australian situation where there is a high background incidence of NMSC the risk will require management.

Heart rate decrease and PR interval prolongation, and interstitial lung disease

The applicant is concerned that the Delegate refers to the Canadian monograph as raising two new issues in relation to the safety of tofacitinib.

The applicant notes the data on heart rate and PR interval were submitted to the TGA in 2013 and reviewed. There were no significant concerns arising from that review. On a related matter the Secretary's Delegate has recorded that it is unlikely tofacitinib prolongs QTc interval based on the review of that package.

Similarly the same data as seen by Health Canada on interstitial lung disease in Asian patients was submitted to the TGA and no particular issues were raised. The applicant has said it will add this as a potential risk to the RMP.

The applicant has indicated it will include wording similar to Canada in the Australian PI for both events.

PI and CMI revisions

The applicant notes that reason 5 refers to 40/58 PI safety related changes and 6/6 safety related CMI changes requested by the Delegate as not been made but that several of these changes related to matters to be considered under this appeal. The applicant is concerned at the suggestion it has not cooperated with the TGA and says, 'The sponsor is well aware of the critical importance of the PI and CMI as tools for risk minimisation and as the basis for other risk minimisation measures described in the tofacitinib RMP (such as HCP education, and Patient Alert card). The sponsor is committed to working with the TGA to ensure the PI accurately informs prescribers about the efficacy and safety of tofacitinib, and provides guidance on appropriate and safe use, and that the CMI is an effective counselling tool to ensure patients are well informed on the use and risks of tofacitinib therapy'.

Safety conclusions

The applicant concludes that the 'safety of tofacitinib has been established in accordance with the legislation and that all applicable regulatory requirements have been met'. The applicant references published requirements (Common Technical Document, EU and other guidelines) and regulatory precedents (relating to bDMARDs approvals) and also the opinions of the three experts who all state that the safety risks of tofacitinib are similar to those of bDMARDs and that Australian rheumatologists will be familiar with managing these. The clinical evaluator's conclusions on safety also across four evaluation reports support that the 'safety profile of tofacitinib overlaps with bDMARDs with regards to risk of infection (including serious infection and opportunistic infection) and malignancy'.

The applicant states that 'Treatment with tofacitinib will be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of RA. The safety risks associated with tofacitinib are intrinsic to immunomodulation therapies in general. In line with current treatment practice, Australian rheumatologists have extensive experience with immunomodulatory treatments and effectively manage the safety as part of routine clinical practice'.

However, the applicant does not provide details of how it will ensure that experienced RA specialists will be the only ones initiation and monitoring therapy with tofacitinib and this is a crucial component of the argument that the safety risk of tofacitinib is manageable in the Australian environment.

The applicant also commits to study long term safety through routine and targeted pharmacovigilance activities with future assessments to include registry studies and a large randomised control trial with a TNFi as a direct comparator.

Efficacy

The applicant expresses concern that in weighting the benefits of tofacitinib the Delegate placed 'undue emphasis' on one endpoint in one trial while 'disregarding data showing clear and compelling evidence in treating signs and symptoms, physical function and the underlying inflammatory process of the disease.'

Clinical trial program considerations

The applicant discussed the five pivotal Phase III studies and the supplementary Phase III study submitted during the evaluation process.

The applicant notes the concerns of the Delegate that the trial populations were too heterogeneous and not reflective of the intended population. However, the applicant references several ICH guidelines (E8[87], E9[88] and E10[89]) dealing with trial design and explains the principle that while earlier phases of drug development are usually highly targeted to maximise the opportunity of identifying a specific effect, Phase III trials are designed to enrol as far as possible populations likely to reflect the real world target. In management of RA it is usual to consider three broad groups of patients for treatment, being those with early RA who are treatment naïve, and those with traditional DMARD failure and then those with bDMARD failure. The latter two categories are not restricted to failure of only one medicine but usually one or more medicines will have been trialled. This is further complicated as tDMARDs may be used in combination. There is also some cross over so that in a very small number of patients in the trials targeting tDMARD failures there had also been a bDMARD failure. Given the realities of management of RA, the trial populations therefore reflected the intended indication as far as practicable.

In discussion of the controls used within trials the applicant notes the European guideline for investigating non NSAID treatment for RA[90], as adopted by the TGA, recommends placebo control but of limited duration of 3-6 months for ethical reasons. The design chosen for the major studies of a two arm study in which both arms receive an established treatment and are then randomised to receive either placebo or the trial drug is one of the designs consider acceptable under this guideline.

The applicant also notes the Delegate's comment that there should be a trial comparing tofacitinib to a bDMARD in the second and third line setting. The applicant notes the guidelines do not require this, nor has it been required of the bDMARDs. However, the applicant does not deny such a study could be of value and notes that it did include a trial incorporating use of adalimumab in the dossier and is planning a large study comparing the safety of tofacitinib and adalimumab/etanercept in a Phase IIIb/IV setting.

Goals of therapy

The applicant quotes the above mentioned guideline on non NSAID treatments for RA as listing the four goals of therapy that may be used for RA as:

- To relieve pain
- To decrease inflammatory synovitis
- To improve or sustain physical function
- To prevent structural joint damage

[87] CPMP/ICH/291/95. ICH Topic E 8. Note for Guidance on General Considerations for Clinical Trials
[88] CPMP/ICH/363/96. ICH Topic E 9. Note for Guidance on Statistical Principles for Clinical Trials
[89] CPMP/ICH/364/96. ICH Topic E 10. Note for Guidance on Choice of Control Groups in Clinical Trials
[90] CPMP/EWP/556/95 rev 1/Final. Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis.

While all goals are important the guideline does not require all be incorporated as measures of benefit in trials. The indication requested by the applicant relates to benefit on signs and symptoms of RA, inflammatory markers and physical function. The applicant notes data on prevention of structural joint damage are also provided.

Efficacy of tofacitinib for the proposed indication

The applicant discussed the major clinical endpoints that are most relevant to the indication. These were the American College of Rheumatology (ACR) response criteria (ACR criteria), the Health Assessment Questionnaire-Disability Index (HAQ-DI) and the Disease Activity Score (DAS) 28.

The applicant explains that HAQ-DI is a patient reported instrument validated to measure functional ability in patients with a wide variety of rheumatic diseases and that ACR criteria and DAS 28 are recognised and validated composite endpoints designed to standardise and address multiplicity issues associated with measuring and reporting of clinical benefit in RA. They are designed to detect improvements in both the underlying disease (inflammation) and the resulting manifestations (signs and symptoms, physical function).

The pivotal trials used ACR20 (defined as at least 20% improvement in tender joint count and swollen joint count and at least 20% improvement in 3 of 5 other measures) as a primary measure and ACR50 and ACR70 as secondary measures.

DAS 28 assesses tender join count and swollen joint count from a list of 28 representative joints, ESR or CRP as acute phase reactant, and the Global Assessment of Arthritis (DAS 28-4)/ For the trials DAS 28-4 (ESR) < 2.6 was used as a primary efficacy parameter, representing remission. As a secondary measure DAS28-4(ESR) ≤ 2.6 was used as a primary efficacy parameter, representing remission. As a secondary measure DAS28-4 (ESR) ≤ 3.2 equates to low disease activity.

The HAQ-DI measures the patient's usual abilities over the last week with a scored ranging from 0 to 3 and a change of ≤ 0.22 units is considered to be clinically relevant. This was used as a primary endpoint and the mean change in HAQ-DI for 5 mg bd tofacitinib was ≥ 0.40 across all studies. Measures of fatigue and health related quality of life were included in secondary endpoints.

Consistent with the findings of the clinical evaluator, the applicant provided data to show that for all primary endpoints listed above there was a statistically significant improvement in the tofacitinib 5 mg bd group over placebo, with the exception of the first time point for DAS28-4 (ESR) in one study though significance was achieved at later time points. In addition, related secondary measures of efficacy showed similar significant benefits.

Effect of tofacitinib on structural progression

The guideline does not require demonstration of effect on structural progression for all products.

The guideline recommends that structural progression should be measured at least one year apart for two years, but contains guidance against using placebo in RA patients for longer than six months. Comparisons to two years are therefore intended to be against the group originally on placebo as the guideline points out ethics would prevent use of a placebo comparator in active RA for greater than six months. The applicant points out that claims of structural benefit have typically followed on from initial approval of bDMARD agents. In its revised indication the applicant has removed reference to an effect on structural progression and therefore does not see the Delegate's concerns about evidence on structural effect as relevant any longer.

The change in the modified Total Sharp Score (MTSS) as six months was used as a primary efficacy measure in one of the five pivotal trials and in the supplementary trial. The score is a recognised radiological measure of structural progression. In Study A3921044 statistically significant improvements in terms of change could not be demonstrated for the 5 mg bd dose at 6 months. The sponsor attributes this to a slower than expected decline in structure for all subjects and notes that there was a trend towards improvement for the active at 5 mg and there were significantly different percentages of patients with no progression at both 6 and 12 months.

In the supplementary study in patients with earlier disease there was statistically significant structure protection from tofacitinib 5 mg bd, but the Delegate did not consider this relevant to the proposed patient population. The applicant argues it and its experts cannot see how it would be biologically plausible for a structural treatment effect to be present at one stage of disease and not another but agree the data is only to twelve months, not two years. The withdrawal of the claim of structural effect makes the issue less relevant for this appeal.

Efficacy conclusions

The applicant summaries that it has 'consistently demonstrated rapid, clinically meaningful and statistically robust improvements with tofacitinib 5 mg bd in reducing disease activity and improving signs and symptoms, functional ability and patient reported outcomes in moderate to severe RA. Clinical benefits have been shown for tofacitinib 5 mg bd across five pivotal studies and one supportive study. They have been observed with tofacitinib when used as monotherapy or in combination with DMARDS including MTX, and in patients at varying stages of disease with varying prior treatment experience. Thus, the clinical trial program and the benefits demonstrated are highly relevant to the Australian RA population and representative of the proposed indication.'

This conclusion would be consistent with that of the clinical evaluation reports concerning efficacy and with the Delegate of the Minister's review of the data with the exception that the majority of combination treatment was with MTX.

Benefit versus risk in the proposed indication

The applicant summarises its argument that the efficacy of tofacitinib has been established for the now proposed indication and the safety profile is similar to those of approved bDMARDs. The applicant states that the safety should be able to be managed appropriately by Australian rheumatologists as the intended prescribers, as they are the group with relevant expertise to manage patients with RA on a potent immunomodulatory treatment.

Reconsideration of the initial decision by the Delegate of the Minister

The Delegate of the Minister for the review noted that section 9A of the Act, which deals with the creation of the ARTG, and paragraph 25(1) of the Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, are of particular relevance.

Findings of fact

An application meeting the requirements of Section 23 of the Act was received on 27 April 2012 and has undergone an evaluation process. During that process the applicant has withdrawn the 10 mg tablet and the Jaqinus trade name.

The Module 3 quality and biopharmaceutic evaluation is complete and there are no issues outstanding.

The Module 4 nonclinical evaluation is complete and the only outstanding issue relating to pregnancy classification for tofacitinib has been resolved satisfactorily as per the PI submitted as part of the pre-ACPM response.

There have been four Module 5 evaluations and five pivotal and one additional major study have been reviewed. There has been consistent evidence of efficacy of tofacitinib 5 mg bd in the treatment of the signs and symptoms of active rheumatoid arthritis, with and without methotrexate, in these studies and this has persisted over time.

Statistically significant evidence of protection against structural damage at the 5 mg dose level was only reviewed at the 12 month mark in a more treatment naïve patient group and the applicant is not pursuing a structural claim at this point.

All evaluations in Australia and by other agencies raised concern at the AE profile which includes serious and opportunistic infections, lymphoma and malignancy concerns, incidence of non melanoma skin cancer, gastric perforation, effect on liver function and creatinine levels and hypertension. The evaluator has concluded these are similar to those seen with bDMARDs and this view is supported by the expert opinion provided and the assessment of several other regulators. There is evidence that the incidence of these adverse effects is stable over time but the applicant has proposed a significant program to investigate safety further and several risk minimisation activities related to the RMP, PI, CMI and HCP educational material in particular. The applicant has also indicated it would like to restrict use to rheumatologists and other specialists physicians experienced in the management of rheumatoid arthritis.

Materials on which the findings of fact were based

The Therapeutic Goods Act (1989) and European Union guidelines adopted by TGA as published on the TGA website.

- The submission for the registration of tofacitinib from Pfizer, including all correspondence to and from the company, additional material submitted during the review, and the appeal documents dated 11 August 2014.
- The TGA evaluation reports and overview documents in respect of the tofacitinib submission.
- The US FDA website pages concerning tofacitinib.
- The Health Canada website pages concerning tofacitinib.
- The EMA website pages concerning tofacitinib.
- Zhang, X., Liang, F. , at al "Tofacitinib for acute rheumatoid arthritis patients who have had an inadequate response to disease-modifying anti rheumatic drug (DMARD): a systematic review and meta-analysis: Clinical Rheumatology 201433 (2) : 165-173.
- Conett, D., Mumford, L. at al "Comparison of the incidence of malignancy in recipients of different types of organs: a UK registry audit" American journal of Transplantation 2010;10: 1889-1896.
- The Australian PI documents at September 2014 for the medicinal products Remicade, Orencia, Humira, Cimzia, Enbrel, Simponi, Actemra, and Mabthera. G.

Reasons

In relation to the requirements set out in Section 25 of the Act:

As set out above, the Delegate of the Minister has reviewed the pharmaceutical chemistry evaluation and Good Manufacturing Practice (GMP) status of manufacturers and does not believe there are any outstanding quality issues.

In relation to the nonclinical data, as set out above, the Delegate of the Minister reviewed the toxicology evaluation and related correspondence and the relevant sections of the proposed PI in the pre-ACPM response and believed there are no outstanding issues and there is nonclinical evidence to support efficacy and safety for the intended use.

As set out above, in relation to the clinical data Delegate of the Minister reviewed the four clinical evaluation reports, the Delegate of the Secretary's Overviews and letter of decision, the ACPM advice and the material provided by the sponsor. Based on the observation of statistically significant, consistent and persistent, treatment effects seen across the six Phase III trials with patients treated out to 3 years, the Delegate of the Minister believed there is evidence of efficacy for the indication proposed in the appeal, thus: *Xeljanz is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had on inadequate response or are intolerant to previous DMARD therapy. Xeljanz can be used alone or in combination with DMARDs, including methotrexate. Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

In reviewing this material the Delegate of the Minister believe there are potential safety issues including those related to serious and opportunistic infections, lymphoma and malignancy, gastrointestinal perforations, alteration in liver enzymes and possibility of drug induced liver injury, development of non melanoma skin cancer, and hypertension. These AEs are consistent with those observed for other agents (bDMARDs) used second line in the management of rheumatoid arthritis.

The Delegate of the Minister noted the intention of the applicant to further investigate the safety of tofacitinib, to monitor its safety in use and to provide educational material to health professionals and patients so as to minimise the risks from AEs, as set out in the proposed revisions to the RMP.

The Delegate of the Minister noted the opinions of the evaluator, ACPM, the Delegate of the Secretary, the rheumatology experts and other regulatory agencies, the majority of which agree that the safety profile is similar to those of agents successfully managed by specialist rheumatologists. The Delegate of the Minister is of the view that experienced Australian rheumatologists should be familiar with the management of these AEs and are best placed to manage patients receiving tofacitinib and that management of these potential AEs would be problematic in non-specialised hands.

The Delegate of the Minister therefore believed that in respect of safety and efficacy for the intended use (see above) when used by relevant specialists with risk minimisation activities in place, the requirement to demonstrate safety and efficacy has been met.

Conclusion

For the reasons referred to above, the Delegate of the Minister decided to revoke the initial decision based on the conclusion that when used by specialist rheumatologists and with the appropriate risk minimisation activities in place, quality, safety and efficacy have been adequately demonstrated for the revised indication as per the appeal documentation.

In order to progress inclusion of the product on the ARTG, the sponsor was requested to submit revised PI and CMI documents consistent with the new indication and the proposed revisions set out in the appeal documents, and a RMP revised in line with the appeal document undertakings. In relation to the risk minimisation activity associated with the restriction of tofacitinib to prescription and monitoring by rheumatologists or specialist physicians experienced in the management of rheumatoid arthritis, the sponsor was asked to consider a short warning at the top of the product information document in black box format to the effect that: *In clinical trials tofacitinib use has been associated with serious und opportunistic infections, and lymphomo and other malignancies have been observed. Therapy with tofacitinib Xeljanz should be initiated and monitored by a*

rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis. Alternately the sponsor could submit a proposal/s on how prescribing will be restricted to appropriate physicians.

Result of the Delegate of the Minister's reconsideration of the initial decision

The Delegate of the Minister decided to revoke the initial decision to not approve Xeljanz (tofacitinib) 5 mg tablets because the Delegate of the Minister was satisfied that the quality, safety and efficacy for the indication,

> *Xeljanz is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. Xeljanz can be used alone or in combination with non-biological DMARDs, including methotrexate.*
>
> *Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.'*

can be satisfactorily established where the appropriate risk minimisation strategies are in place.

Final outcome

The Delegate was of the view that the requirements of efficacy and safety in the Act have been met to include the Xeljanz tofacitinib (as citrate) 5 mg tablets in the ARTG. The reasons for the Delegate's decision and results of the reconsiderations of the initial decision are set out above.

Accordingly, the Delegate of the Secretary under section 25AB of the *Therapeutic Goods Act 1989* ("the Act") decided, under subsection 25(3) of the Act, to approve the registration of Xeljanz tofacitinib (as citrate) 5 mg tablet blister and bottle, for the indications:

> *Xeljanz is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. Xeljanz can be used alone or in combination with nonbiological DMARDs, including methotrexate.*
>
> *Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

This approval was based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application and as part of the appeal under section 60 of the Act dated 11 August 2014.

Specific conditions of registration applying to these therapeutic goods

- The Xeljanz tofacitinib Australian Risk Management Plan (RMP), version 1.3, dated 10 December 2014, included with the appeal under section 60 of the Act and email correspondence dated 12 December 2014, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.
- The sponsor should notify and provide copies of all amendments to education material for health professionals and patients to the Office of Product Review in the TGA prior to distribution. The current version submitted with RMP version 1.3, dated 10 December 2014 is acceptable.

Attachment 1. Product Information

The Product Information approved for Xeljanz at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report: First and second rounds

Attachment 3. Extract from the Clinical Evaluation Report: third round

Attachment 4. Extract from the Clinical Evaluation Report: fourth round

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au