Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Tofacitinib (as citrate)

Proprietary Product Name: Xeljanz

Sponsor: Pfizer Australia Pty Ltd

May 2018

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 <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (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; it provides 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

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ACR	American College of Rheumatology
AE	Adverse Event
AIAS	All-Available Immunogenicity Analysis Set
AUC	Area Under Concentration-Time curve over the dosing interval
CCP	Cyclic Citrullinated Peptide
CD	Cluster of Differentiation
CI	Confidence interval
Cmax	Maximum serum drug concentration
CPK	Creatine Phosphokinase
CRP	C-Reactive Protein
CS	Corticosteroids
DAS	Disease Activity Score
DMARD	Disease Modifying Anti-Rheumatic Drug
EIAS	Evaluable Immunogenicity Analysis Set
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
ES	Erosion Score
ESR	Erythrocyte Sedimentation Ratio
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FDA	Food and Drug Administration (US)
GMFR	Geometric Mean Fold Rise
HAQ-DI	Health Assessment Questionnaire – Disability Index
IL	Interleukin

Abbreviation	Meaning
Ig	Immunoglobulin
JAK	Janus Kinase
JSN	Joint Space Narrowing
LEP	Linear Extrapolation
LS	Least Squares
LTE	Long Term Extension
mTSS	modified Total Sharp Score
MTX	Methotrexate
NK	Natural Killer
NRI	Non Responder Imputation
NSAID	Non-Steroidal Anti-Inflammatory Drug
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PBO	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
PY	Patient-Years
RA	Rheumatoid Arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Score
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
TB	Tuberculosis
TOF	Tofacitinib Citrate
ULN	Upper Limit of Normal

Abbreviation	Meaning
VZV	Varicella Zoster Vaccine

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	1 June 2017
Date of entry onto ARTG:	6 June 2017
ARTG numbers:	196987, 233439
Active ingredient:	Tofacitinib (as citrate)
Product name:	Xeljanz
Sponsor's name and address:	Pfizer Australia Pty Ltd 38-42 Wharf Road West Ryde NSW 2114
Dose form:	Immediate release tablet
Strength:	5 mg
Containers and pack sizes:	HDPE bottles with silica gel desiccant and child-resistant caps containing 60 or 180 film coated tablets. Aluminium foil/PVC backed aluminium foil unit dose blisters containing 56 film coated tablets.
Approved therapeutic use:	*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 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.*
Routes of administration:	Oral

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd to extend the indications of Xeljanz (tofacitinib [TOF]) rheumatoid arthritis (RA) indication to include a claim of inhibition of structural damage, as measured by plain sequential x-ray, for the approved RA treatment population (that is in adult patients with a preceding inadequate response to or intolerance of methotrexate [MTX]). As noted by the clinical evaluator, an impact on inhibiting the structural bone damage of RA is associated with better long term patient outcomes particularly regarding maintenance of physical function and quality of life. In addition, the submission seeks to update the PI with the latest safety information.

TOF is a selective inhibitor of the Janus kinase (JAK) family of kinases, with greater inhibition of JAK1 and JAK3, than JAK2 and tyrosine kinase 2. The JAK system is an intracellular pathway regulatory system that affects the release of cytokines and amplification of the inflammatory response. TOF preferentially inhibits signalling by heterodimeric receptors associated with JAK1 and JAK3, thereby blocking the production and signalling of several pro-inflammatory cytokines including IL-1, 2, 4, 6, 7, 9, 15 and 21 as well as type 1 interferon. In combination, these effects decrease lymphocyte activation, proliferation and function, which are key immune response targets in successfully treating active RA.

The Advisory Committee on Prescription Medicines (ACPM) considered tofacitinib in February 2014. At that time, the ACPM considered that there was insufficient evidence of an effect on retarding structural progression for the TOF 5 mg twice daily (BD) dose in combination with MTX in the proposed treatment population. The application for tofacitinib for 5 mg and 10 mg for the RA indication was initially rejected after lengthy discussions with the sponsor, predominantly regarding safety concerns with the 10 mg BD dose. The sponsor withdrew its application to register the 10 mg dose during those discussions. The sponsor appealed the decision for the 5 mg BD dose, and later gained approval for the 5 mg BD dose. The approved treatment indication removed the original sponsor claim of radiographic benefit. The sponsor is now requesting that the claim of radiographic benefit with tofacitinib be included based on the current submission.

The Xeljanz (tofacitinib) 5 mg tablet was entered on the ARTG on 5 February 2015. The following indication has been approved in Australia:

> *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.*

The European Committee for Medicinal Products for Human Use (CHMP) refused the application for marketing authorisation of tofacitinib 5 mg BD and 10 mg BD doses for the treatment of rheumatoid arthritis on 25 April 2013 and re- confirmed the refusal on 25 July 2013. The grounds for refusal included significant and unresolved concerns about the overall safety of tofacitinib, particularly regarding the risk and type of serious infections and other serious adverse effects such as malignancy, gastrointestinal perforation, liver damage and increased blood lipid levels. EMA were uncertain if these risks could be successfully managed. Regarding the efficacy data, EMA decided that tofacitinib had evidence that it improves the symptoms and signs of RA as well as physical functioning of patients, but there was insufficient evidence that it consistently reduced disease activity and joint structural damage, particularly at the 5 mg BD dose and in patients in whom at least 2 DMARDs had been tried. Following extensive consultation with European regulators and additional analyses to address the grounds for refusal, a new application was submitted to EMA in March 2016. On 26 January 2017, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Xeljanz, for the treatment of RA. Xeljanz was approved in the EU on 22 March 2017. The approved SmPC indication is worded as follows:

> *Xeljanz in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. Xeljanz can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see sections 4.4 and 4.5).*

The tofacitinib 5 mg immediate release (IR) and the tofacitinib 11 mg extended release (XR) formulations are approved in the US. The following indication was approved in the US for both formulations:

> *Xeljanz/Xeljanz XR 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).*

The tofacitinib 5 mg IR formulation is approved in Canada. The following indication for the IR formulation was approved in the Canada:

> *Xeljanz (tofacitinib) is combination with methotrexate (MTX), is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA), in adult patients with moderately to severely active RA who have had an inadequate response to MTX.*
>
> *In cases of intolerance to MTX, physicians may consider the use of Xeljanz (tofacitinib) as monotherapy.*

At Round 1, the sponsor indicated that the radiographic dataset had been submitted in the EU, the US and Singapore and that submission in 2016 was planned for Canada and Switzerland. A new medicine application for tofacitinib was under review in New Zealand.

The EU guidelines adopted by the TGA relevant to this submission, in addition to the general guidelines are:

- CPMP/EWP/556/95 rev 1/Final Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for the Treatment of Rheumatoid Arthritis

These guidelines state that:

> *In order to demonstrate efficacy in radiological terms using technology currently generally available, an observation period of not less than 1 year is required. The observation period needed is not less than two years, showing sustained effects for the effects after the first year.*

Regulatory status

The international regulatory status at the time of submission is listed in Table 1. The pivotal dataset supporting this extension of indications application consists of two Phase III studies, A3921069 and A3921044, which investigated the effect of tofacitinib on structural progression in adults with active RA. Table 1 provides dates of submission (if available) of this 'radiographic dataset'' and the regulatory status in countries of interest to TGA.

Table 1: International regulatory status

Country / region	Submission date	Status	Indications (approved or requested)	Other relevant information
EU (centralised procedure)[1]	4 March 2016; Procedure	Positive CHMP Opinion:	Xeljanz in combination with methotrexate	Clinical data for radiographic

1 In October 2011, a Marketing Authorisation Application (MAA) was submitted in Europe via the centralised procedure to register tofacitinib but, for reasons previously described to the TGA in detail during the Australian registration process, was not granted. Following extensive consultation with European regulators

Country / region	Submission date	Status	Indications (approved or requested)	Other relevant information
Rapporteur: UK MHRA; Co-rapporteur: Italy AIFA	start: 24 March 2016	26 Jan 2017	(MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more diseasemodifying antirheumatic drugs. Xeljanz can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see sections 4.4 and 4.5).	response: Results from both studies A3921069 and A3921044 are included in Section 5.1 of the SmPC.
US	22 April 2013	Approved: 21 Feb 2014	Xeljanz (tofacitinib) is 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). Limitations of Use: Use of Xeljanz in combination with biologic DMARDs or with potent immunosuppressa	Clinical data for radiographic response: Results from both studies A3921069 and A3921044 are included in Section 14 of the approved USPI.

and additional analyses to address the grounds for refusal, a new MAA was submitted in March 2016 which included the radiographic dataset.

Country / region	Submission date	Status	Indications (approved or requested)	Other relevant information
			nts such as azathioprine and cyclosporine is not recommended.	
Canada[2]	Planned for 2017			
Switzerland[3]	Planned for 2017			
New Zealand	N/A for radiographic indication	NMA for product registration is currently under review		
Singapore	20 May 2013	Approved: 17 Nov 2014	Xeljanz (tofacitinib) in combination with methotrexate (MTX), is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA), in adult patients with moderately to severely active RA who have had an inadequate response to methotrexate. In cases of intolerance to methotrexate, physicians may consider the use of Xeljanz (tofacitinib) as monotherapy.	Clinical data for radiographic response: Results from both studies A3921069 and A3921044 are included in Section 5 of the approved foreign PI.

[2] Inclusion of a radiographic claim and data in the foreign PIs was not accepted at the time tofacitinib was initially registered in those markets. Plans for re-submission of the radiographic data are underway.
[3] Inclusion of a radiographic claim and data in the foreign PIs was not accepted at the time tofacitinib was initially registered in those markets. Plans for re-submission of the radiographic data are underway.

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. Registration timeline

The regulatory timeline of this submission is detailed in Table 2.

Table 2: Regulatory timeline of this submission

Description	Date
Submission dossier accepted and 1st round evaluation commenced	6 Jun 2016
1st round evaluation completed	1 Nov 2016
Sponsor provides responses on questions raised in 1st round evaluation	6 Jan 2017
2nd round evaluation completed	7 Feb 2017
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	3 Mar 2017
Sponsor's pre-Advisory Committee meeting response	21 Mar 2017
Advisory Committee meeting	6-7 Apr 2017
Registration decision	1 Jun 2017
Entry onto ARTG	6 Jun 2017
Number of TGA working days from submission dossier acceptance to registration decision *	193

* Legislative timeframe for standard applications is 255 working days (see *Therapeutic Goods Regulations 1990*).

III. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Information on the condition being treated

RA is a chronic inflammatory autoimmune disease characterised by polyarticular inflammation of predominately small to medium sized joints in a symmetric pattern. The condition affects approximately 1% of the Australian population and its prevalence increases with age. The primary lesion is synovitis whereby immune cells invade the normally acellular synovium leading to the formation of inflammatory pannus. This hyperplastic invasive tissue causes cartilage breakdown, bony erosion and ultimately loss of function of the affected joints. Systemic involvement may also occur, and there is an increased risk of atherosclerosis and lymphoma over time, particularly if the condition is insufficiently controlled. The over production of various pro-inflammatory cytokines such as TNF and interleukins in the joints and sera of patients with RA are important mediators in the disease pathogenesis primarily via activation of T lymphocytes, but also through effects on B lymphocytes.

Current treatment options

RA is a heterogeneous condition in terms of clinical presentation, natural history and drug responsiveness. Published evidence and current guidelines for the treatment of RA emphasise the importance of achieving clinical remission, or at least low disease activity, as both of these states are associated with a favourable long term prognosis. In addition to treating the signs and symptoms of RA, an impact on inhibiting the structural bone damage of the condition is highly desirable as this is associated with better long term patient outcomes, particularly regarding maintenance of physical function and quality of life. Conventional synthetic DMARDs (in particular, MTX), alone or in combination with each other, are the initial recommended treatments for RA. Observational studies and meta-analyses of DMARD treatment efficacy and tolerability demonstrate highly variable outcomes to single and combination DMARD therapy over time. In 10-year follow-up studies, 25% of patients with RA had to discontinue conventional DMARD treatment due to insufficient therapeutic benefit and 20% discontinued treatment due to adverse effects. Biological DMARDs, either as add-on or single drug therapy, is the next recommended line of therapy in active RA after conventional synthetic DMARD failure or intolerability. While anti-TNF drugs and cytokine modulators such as abatacept and tocilizumab have been shown to demonstrate significant efficacy in treating active RA, a substantial proportion of patients are not achieving meaningful American College of Rheumatology (ACR) responses. Based on the current literature for biological therapies, ACR20 response rates range from 50 to 65% and ACR50 response rates are 35 to 50%. As such, there is a need for additional therapies for active, treatment refractory RA in adult patients.

Clinical rationale

TOF is a selective inhibitor of the JAK family of kinases, with greater inhibition of JAK1 and JAK3, than JAK2 and tyrosine kinase 2. The JAK system is an intracellular pathway regulatory system that affects the release of cytokines and amplification of the inflammatory response. TOF preferentially inhibits signalling by heterodimeric receptors associated with JAK1 and JAK3, thereby blocking the production and signalling of several pro-inflammatory cytokines including IL-1, 2, 4, 6, 7, 9, 15 and 21 as well as type 1 interferon. In combination, these effects decrease lymphocyte activation, proliferation and function, which are key immune response targets in successfully treating active RA.

Guidance

The sponsor states that this submission is consistent with the TGA pre-submission planning process. An exchange of pre-submission briefing documents between the sponsor and TGA occurred between March and April 2016. The objectives of the pre-submission planning process were:

- to provide an update on the status of any overseas registration applications, particularly re-submission to the EMA, including proposed treatment indication wording and dose regimens,
- to clarify that the sponsor is not requesting a change in Australia to the approved RA treatment population (that is TOF is currently approved in those with an inadequate response or intolerant of MTX versus subjects who are MTX naïve as per the enrolment characteristics of Study A3921069 in this submission),
- to provide an updated version of the Australian Risk Management Plan (RMP), and
- to clarify if the 2 year radiographic dataset has been submitted to the FDA and if it is to be included in the US PI.

Following the pre-submission questions, the sponsor responded to each issue. In particular, the sponsor re-affirms that it is not requesting a change in the current patient treatment indication claim in Australia. This submission is requesting the addition of a radiographic claim of benefit to the same approved patient inclusion criteria (that is in adult patients with a preceding inadequate response to or intolerance of MTX).

Consideration of the relevant regulatory guidelines in assessing this submission includes one specific and relevant EU regulatory guideline pertaining to the requested indication in RA: CPMP/EWP/556/95 rev 1/Final 'Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for the Treatment of Rheumatoid Arthritis' (effective 29 January 2007). In this submission, the 2 year study reports for 2 pivotal Phase III RA studies (A3921044 and A3921069), which assessed the rate of joint damage progression by plain x-ray, has been submitted. The TGA adopted EU regulatory guideline (CPMP/EWP/556/95 rev 1/Final) states that to make a claim of radiographic benefit in RA, x-ray should be taken at fixed and pre-defined time points at least 1 year apart for a minimum of 2 years, the first year of which should have blinded data acquisition.

Evaluator's commentary on the background information

TOF is a first in class JAK inhibitor currently approved in Australia for the treatment of active RA in adult patients. It is available as an oral formulation and exerts an immunomodulatory effect via a novel mechanism of action. There is an unmet need for additional effective therapies in RA as response rates to current available treatment options (including several conventional and biological DMARDs) are sub-optimal in a significant proportion of patients (that is at least one third of affected individuals with moderately to severely active disease). Through intracellular inhibition of JAK pathways and subsequent modification of the inflammatory response, TOF demonstrates biological plausibility for producing a beneficial treatment effect in RA.

In recent years, published evidence has supported a significant clinical practice change in treating RA whereby tight and sustained control of disease activity is the desired outcome. In addition to controlling the signs and symptoms of RA, it is recognised that inhibition of structural x-ray progression is a very important outcome as achievement of this outcome strongly correlates with minimisation of joint deformity and physical functioning. Hence, the sponsor has stated a valid and accepted rationale for the relevance of claiming structural x-ray inhibition in this submission.

In general, the sponsor has adhered to the TGA adopted EU regulatory guideline of relevance in this submission (CPMP/EWP/556/95 rev 1/Final 'Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for the Treatment of Rheumatoid Arthritis'; effective 29 January 2007). However, in the Clinical Trials section of the newly proposed PI, the sponsor has included x-ray data suggesting benefit with TOF monotherapy in MTX naïve subjects (as reported in Study A3921069), which is different to the approved treatment population (that is MTX inadequate response or intolerance).

As outlined in the regulatory history background of this report, the TGA had initially rejected the registration of TOF for the treatment of RA (at a dose of 5 mg and 10 mg twice daily), but the sponsor under Section 60 of the *Therapeutic Goods Act* appealed this decision. Following review, the TGA decision to not register TOF was revoked and TOF was approved on 13 January 2015 at a dose of 5 mg twice daily. Therefore, to support a radiological claim being added to the current indication wording the sponsor must demonstrate that a TOF dose of 5 mg twice daily has robust x-ray evidence of benefit over 2 year treatment time frame (as per the TGA adopted EU guideline) in the population for which it is currently approved (patients with an inadequate response to or who are intolerant of MTX). In this submission, the sponsor has responded to the prior key issues that have impeded the registration of TOF in Australia and overseas (namely, the EU). The previously considered safety concerns with TOF include: the incidence and type of serious and opportunistic infection, gastrointestinal perforation, malignancy potential (particularly, lymphoma and pancreatic cancer), risk of developing interstitial lung disease, cytopenia, hepatic enzyme elevations/drug induced liver injury, elevations in serum lipids (with an atherogenic profile) and the risk of major adverse cardiovascular events.

Contents of the clinical dossier

The 2 main purposes of this application by the sponsor is to consider inclusion of the efficacy claim in the indication wording relating to the inhibition of structural damage progression, and to update the safety information in the PI with available data as of 31 March 2015.

This report summarises the extensive background Australian regulatory history that predates this submission. The new efficacy data included in this submission is the 2 year results from Study A3921069 (not previously evaluated by TGA), as well as additional sensitivity analyses of the x-ray data from Study A3921044 and subgroup analyses of patients with poor prognostic factors enrolled into Study A3921044. The sensitivity analyses of the x-ray data in Study A3921044 were presented in a summary format during the initial evaluation process, however, with this submission a more thorough assessment is presented, which is complemented by a subset analysis in second line patients, defined as those who were inadequate responders to or intolerant of MTX, but naïve to biologic therapies.

Persistence of clinical response to TOF (that is improvement in the signs and symptoms of RA) is provided in this submission by the 2 year clinical trial reports for Studies A3921044 and A3921069, as well as additional data from 2 open label, extension studies (one completed [A3921041] and one ongoing [A3921024]), which followed patients receiving TOF 5 mg twice daily therapy for up to 84 months (7 years).

This submission also proposes to update the safety information in the PI following a review of the available safety dataset as of 31 March 2015, as well as incorporate the information derived from the completed Study A3921237, which assessed the effect of TOF 5 mg twice daily on the zoster vaccine immune response in adult subjects with RA receiving concomitant MTX.

Paediatric data

EMA and FDA have granted a waiver for the treatment of chronic juvenile idiopathic arthritis for children from birth to less than 2 years of age as the conditions for which TOF is intended rarely occur in this age group. However, a paediatric investigation plan for the treatment of several types of juvenile idiopathic arthritis (including extended oligoarthritis, RF+ve polyarthritis, RF-ve polyarthritis, enthesitis related arthritis, psoriatic arthritis and systemic arthritis) for children from 2 to 18 years of age has been agreed.

Good clinical practice

Apart from a couple of noteworthy exceptions, the studies presented in this submission are stated to have been conducted according to GCP standards and the study reports are consistent with adherence to GCP. The pivotal radiographic Study A3921044 was conducted at 110 investigator sites in 15 countries. One study centre in India was prematurely closed during the trial due to GCP non-compliance during an internal sponsor audit. This site had screened 22 subjects, 8 of whom were randomised to treatment and 3 had discontinued prior to site closure. The efficacy data from this site was excluded from analysis but the safety data for the 8 randomised subjects was included. In addition, 1 study site in Study A3921044 in Korea had significant procedural issues, which led to its closure after 3 months of study involvement. Efficacy data from this site was also excluded from the analysis. The sponsor due to non-compliance issues with GCP closed one study centre in the Philippines in Study A3921069, but this was only identified after the study was completed. The efficacy data from this site was excluded but analysis with or without that information showed minimal effect on the overall efficacy data.

Evaluator's commentary on the clinical dossier

The sponsor designed the TOF RA clinical development program to demonstrate safety and tolerability; as well as efficacy in reducing the signs and symptoms of RA, inhibiting the progression of structural damage and improving physical function. The clinical program includes 6 randomised, multi-centre, double blind, parallel group Phase III studies evaluating the efficacy and safety of TOF in a variety of RA treatment settings. The predominant treatment algorithm in the clinical development program was the addition of TOF to inadequately effective conventional synthetic DMARDs (mainly, prior MTX therapy). Additional studies were conducted to assess TOF efficacy as monotherapy, replacing rather than adding to a previous DMARD, in subjects who had an inadequate response to a biologic DMARD, and to assess the efficacy of TOF as monotherapy in MTX-naïve subjects.

In this application, the pivotal Phase III studies are A3921069 and A3921044. Data pooled from the 2 LTE studies (Study A3921024, which is ongoing and Study A3921041, which is completed) were also used to inform long term safety and persistence of clinical efficacy with TOF in treating RA. Unfortunately, the sponsor only presented in this submission combined safety data from the LTE studies when changes to the PI were proposed. Clinical study reports (interim for A3921024 and complete for A3921041) were provided for each trial, but the safety data required significant synthesis as it was not well presented.

For other safety events of interest (for example risk of serious infection), the sponsor provided integrated data from all of the RA controlled (Phase I, II and III) and LTE studies, but this was done on ad hoc basis when changes to the PI were proposed. Comprehensively responding to each safety sub-section would have been a more rigorous way to present the data for independent evaluation. The sponsor also included results from a Phase II study (A3921237) evaluating the effect of TOF 5 mg twice daily on the

zoster vaccine immune response in patients with RA. This study's results were presented separately in a clear manner, which was appropriate.

Pharmacokinetics

Studies providing pharmacokinetic data

No new PK data was provided in this submission.

Evaluator's conclusions on pharmacokinetics

The PK properties of TOF in adult patients with active RA have been previously assessed. No new PK data was provided in this submission and the sponsor is not proposing any changes to the PK section of the current PI.

Pharmacodynamics

Studies providing pharmacodynamic data

The PD properties of TOF in adult patients with active RA have been previously assessed in the original TGA submission. However, in this submission, the sponsor has included a previously unevaluated, exploratory Phase II Study (A3921073) that had the primary objective of examining the PD effects of oral TOF 10 mg twice daily over 4 weeks in adults with active RA. The effect of TOF therapy upon synovial tissue biopsy and serum biomarkers of interest was examined in this trial. However, the sponsor is not proposing any changes to the PD section of the current PI based upon data observed in Study A3921073.

In addition, the sponsor has included new data from an ongoing, open label, long term extension Study (A3921024) in which lymphocyte subset cell counts was collected for a median duration of 5 years in TOF treated subjects. The sponsor has included this new data as part of the proposed amendments to the PI (Pharmacology section) with this submission.

Evaluator's conclusions on pharmacodynamics

TOF is a potent inhibitor of JAK1 and JAK3 and a moderate inhibitor of JAK2. The impact of these inhibitions is primarily on the immune (T cell function) and haematological systems. Studies (clinical and non-clinical) clearly demonstrate potent inhibition of T-cell proliferation and differentiation, and significant effects on NK cells. The newly submitted Phase II Study (A3921073) shows that treatment with TOF 10 mg twice daily in conjunction with continued weekly low dose MTX has a wide range of beneficial effects on the synovial tissue and serum biomarkers of RA. In particular, TOF therapy impacts upon the bone and cartilage turnover markers of active RA (dampening their over-activity), which supports the biologic plausibility that TOF may produce a beneficial effect on reducing the structural progression of active RA.

Dosage selection for the pivotal studies

The dose response relationship has been assessed in 5 Phase II studies and these results informed the dosage selection in the pivotal Phase III trials. This data has already been evaluated in the original TGA submission and the sponsor is not proposing any changes to the approved posology (TOF 5 mg twice daily by oral administration). The Phase II studies

were conducted in diverse populations of DMARD inadequate responders with active RA and examined a TOF dose range of 1 to 30 mg twice daily for durations ranging between 6 and 24 weeks in over 1,500 subjects. The selection of the TOF 5 mg and 10 mg twice daily regimens examined in the Phase III studies was primarily based on the dose-response modelling of safety and efficacy data in Study A3921025. This trial demonstrated a relationship between efficacy (ACR20/50/70 response rates) and dose, as well as adverse effects (namely, changes in haemoglobin levels) and dose. No other safety parameters such as changes in lymphocyte cell counts and risk of infection were considered in the dose selection analysis.

In both pivotal x-ray studies, the mean and median doses of background treatment with conventional DMARD therapy (MTX) over the entire treatment period were not provided. This is a limitation of the dataset as further information is required to determine the adequacy of comparator treatment and its consistency with contemporary clinical practice in Australia. Recent expert opinion concludes that such prior and/or concurrent therapy reflects sub-optimal practice before the commencement of biologic therapy in patients with active RA.[4] In particular, the maximal concurrent dose of MTX should be used in the comparator arm of all biologic therapy trials (up to 25 mg/week, by the SC route if dose > 15 mg/week for MTX) as sub-optimal MTX dose in the comparator arm may bias efficacy results in favour of biological agents. Moreover, low dose oral corticosteroid (prednisone ≥ 10 mg/day) and NSAID use was recorded in approximately two-thirds of all patients (equally dispersed among the treatment arms) in the 2 pivotal TOF studies, which reflects appropriate concomitant drug use in individuals with active RA, and is consistent with prescribing patterns in Australia.

The comparator treatment in Study A3921069 was low dose, weekly MTX and the trial recruited patients who were predominantly naïve to DMARD therapy (approximately 60% in total). The choice of low dose weekly MTX as the active comparator is of limited value in assessing the sponsor claim of TOF inhibiting structural radiographic progression. The approved treatment indication for MTX in patients with RA does not make a claim of radiographic benefit, thus the comparator is not appropriate for the proposed x-ray claim. The recommended comparator for TOF in making a claim of structural benefit in RA is a drug (anti-TNF or other biologic DMARD) that is already approved for that claim, assessed by a head-to-head, non-inferiority study design.

Efficacy

Studies providing efficacy data

Radiographic data from 2 pivotal studies, one in a first line treatment population (Study A3921069) and the other in a second line treatment population (Study A3921044) have been submitted as evidence that TOF is an effective DMARD in inhibiting the progression of structural joint damage in adult patients with active RA. The current approved treatment indication in Australia places TOF as a second line therapy as the wording states that TOF is indicated in adults who have an inadequate response to or are intolerant of MTX. In this submission, the sponsor is not requesting a change to its place in therapy (that is TOF remains a second line treatment option).

X-ray and clinical efficacy data had already been evaluated in the original TGA submission. The focus of the efficacy assessment in this clinical evaluation report will be 2 fold: to evaluate the extended radiographic dataset (12 and 24 month x-ray data) to assess the newly proposed indication claim of inhibition of progression of structural damage; and the

[4] Durán J, et al. Methotrexate dosage as a source of bias in biological trials in rheumatoid arthritis: a systematic review. *Ann Rheum Dis.* 75: 1595-8 (2016).

durability of clinical efficacy outcomes with continued TOF therapy as this data has been included in the updated PI.

Evaluator's conclusions on efficacy

In support of the extension of treatment indication for TOF to include a claim of radiographic benefit in patients with RA, this submission contains two Phase III studies (A3921044 and A3921069), both of which were nominated as pivotal by the sponsor. The 2 studies were of dissimilar design and recruited very different treatment populations. Study A3921044 enrolled 797 subjects with established RA (mean disease duration of approximately 9 years) who were inadequate responders to at least 4 months of preceding MTX and approximately 20% of patients had previously been exposed to biologic DMARD. Study A3921044 had 3 treatment arms (2 with 2 different doses of TOF; 5 mg and 10 mg twice daily) and a control group, which escaped or mandatorily switched to TOF therapy between 3 and 6 months. All subjects in this trial continued to receive MTX concomitantly throughout the study. In contrast, Study A3921069 was a TOF monotherapy trial of 2 different doses of TOF (5 mg and 10 mg twice daily) versus weekly, low dose MTX in 956 subjects who had early disease (median duration of 0.8 years) and who were largely naïve to MTX. Both of the Phase III studies are completed with final study reports up to 24 months of treatment follow-up being included in this submission. The majority of patients (approximately two thirds) in both Phase III trials completed 2 years of follow-up. However, in Study A3921044 where the control arm were eligible for switching to TOF as early as 3 months, approximately half of all PBO treated patients switched to TOF as they were considered clinical non-responders. At 6 months in Study A3921044, all continuing PBO treated subjects were switched to either dose of TOF in the maintenance treatment phase (between 6 and 24 months).

Both of the Phase III studies were randomised, double blinded and parallel group controlled in design and enrolled adult patients with a confirmed diagnosis of RA. Subjects were required to have moderate-severe disease activity at baseline with the BASDAI score being ≥ 6 tender and swollen joints and have raised serum inflammatory markers (CRP> 7 mg/L) and/or joint erosions or positive autoantibody tests at baseline. Both of the Phase III studies had the mean change from baseline to 6 months in the mTSS as the primary radiographic endpoint. The baseline demographic and disease related characteristics of patients in the Phase III trials are diverse but similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. The majority of patients were female, of Caucasian ethnicity, and within the expected age range of 45 to 65 years. However, there are some caveats to the generalisability of the treatment population. For example, both studies excluded patients who were at a significant risk of infection or malignancy, or who had various abnormal laboratory results at baseline (for example abnormal haematology or liver function tests).

This submission is seeking an indication of structural benefit in active RA and is generally consistent with the TGA adopted regulatory guideline pertaining to the requested extension of indication: EU guideline CPMP/EWP/556/95 rev 1/final 'Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for the Treatment of Rheumatoid Arthritis' (effective 29 January 2007). However, neither of the Phase III trials directly evaluated TOF against an already approved drug for the x-ray indication such as anti-TNF therapy. The choice of comparators (MTX in Study A3921069 and PBO + continued MTX in Study A3921044) for the claim of radiographic is an area of significant contention, which is not specifically addressed in the TGA adopted EU guideline. However, there is no precedent for the registration of a biologic drug currently approved for a radiographic claim in RA to have conducted head-to-head studies. For both Phase III

studies, the choice of x-ray efficacy endpoints (primary and secondary), and strategies to maintain blinding and randomisation procedures were suitable.

The primary efficacy endpoint in both Phase III studies was the LS mean change from baseline to 6 months in the mTSS. The pre-specified secondary x-ray efficacy endpoints included the component scores of the mTSS and the proportion of subjects with no x-ray progression (defined as change form baseline of ≤ 0.5 sharp units). X-ray endpoints were evaluated at months 6, 12 and 24. The supporting exploratory Phase II Study A3921068 also evaluated MRI data of the peripheral joints in association with plain radiography changes over 6 months in a group of treatment naïve patients with early disease (n = 109 subjects). Both the Phase III studies also provided efficacy data up to 24 months in support of the maintenance of treatment effect.

Study A3921069 demonstrated that both doses of TOF monotherapy (5 mg and 10 mg twice daily) produced statistically significant structural preservations benefits compared to MTX, across the range of primary x-ray efficacy measures (LS mean change from baseline in mTSS) and secondary x-ray measures of response (LS mean changes from baseline in ES and JSN scores as well as the proportion of subjects with no x-ray progression) at 6, 12 and 24 months.

In contrast, Study A3921044 (that is in a predominantly second line treatment population) did not show a significant x-ray treatment benefit with TOF 5 mg twice daily versus control therapy in the primary statistical analysis which used LEP for handling of data. However, when the 6 and 12 month x-ray dataset for Study A3921044 (Campaign 1) had analyses applied to the data that reduced the effect of extrapolation and utilised more observed (non-extrapolated) data than in the primary analysis, statistically significant reductions in structural damage progression for both TOF doses were observed compared to PBO. However, many of these sensitivity and secondary analyses were post hoc in nature and their utility is guarded with respect to supporting a scientifically robust conclusion. The evaluator agrees with the sponsor that that low rates of structural damage progression, the short treatment period before treatment advancement was required (3 or 6 months), and the large proportion of PBO treated subjects advancing at the Month 3 time point may have resulted in the initial analyses being more sensitive to data anomalies such as large change from baseline values at the extremes of the distribution of change scores or to the effects of extrapolation. However, this is unfortunate consequence of the study design and conduct. The sponsor also suggests that the mean changes from baseline in mTSS at 6 and 12 months for TOF 5 mg twice daily therapy (Study A3921044) are of a similar magnitude to those observed with tocilizumab and at least 2 anti-TNF therapies, all of which have an approved x-ray claim in RA. However, indirect data comparisons such as these are fraught with interpretation.

The clinical efficacy data available up to 24 months in both Phase III studies indicated that the majority of responding patients appear to maintain their treatment related benefit with continued TOF. In addition, for PBO patients who switched to TOF at 3 to 6 months in Study A3921044, the rates of ACR response observed at 12 and 24 months were similar to those achieved in the originally treated TOF cohort. Like the Phase III studies, the open label, LTE Studies A3921024 and A3921041 showed that clinical efficacy was maintained in the majority of subjects up to 7 years with continued TOF 5 mg twice daily therapy.

Overall, the data in this submission provides an unclear picture on the radiographic efficacy of TOF 5 mg twice daily therapy for inhibiting the x-ray structural progression of RA, in those with moderate-severely active disease at baseline, with or without concurrent MTX. In the DMARD naïve group of patients with early disease (Study A3921069), the magnitude of beneficial x-ray response with TOF versus MTX is small, but statistically significant. Treatment related x-ray differences between TOF and PBO in the second line treatment population (as per Study A3921044 and consistent with TOF current registration status in Australia) is of unclear magnitude and only reached statistical

benefit when sensitivity and subset analyses were applied to the dataset, which had its limitations for various reasons.

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

Study A3921237 is a newly submitted Phase II trial of 14 weeks duration (12 weeks of study treatment), which primarily assessed immune responses (humoral and cell mediated) following administration of zoster vaccine to subjects aged at least 50 years (n = 112 subjects) with active RA receiving TOF or PBO with background MTX treatment. Immunogenicity and clinical safety data from this study will be presented separately in this report. The trial did not specifically collect efficacy data.

Pivotal and/or main efficacy studies

In the registration application for TOF, the interim 1 year results of Study A3921069 were evaluated, but the final 2 year clinical study report was deemed to have been submitted too late in the process and therefore was not evaluated in detail. The full 24 month safety dataset from Study A3921069 will be considered in this report.

The following safety data was collected in Study A3921069 (as well as the other pivotal efficacy studies of the program):

- Adverse Events (AEs) in general were assessed by completion of the AE Case Report Form (CRF) and physical examination performed every 4 weeks until month 3, and then every 3 months thereafter up until month 24 (or upon early withdrawal).
- AEs of particular interest, including infections (overall and serious), gastrointestinal perforation, malignancy, interstitial lung disease, Major Adverse Cardiovascular Events (MACE) and drug induced liver disease were assessed by CRF and physical examination as per the schedule for general AE evaluation.
- Laboratory tests, including haematology, clinical chemistry, and urinalysis and urine pregnancy testing (in female subjects) were performed at baseline, every 4 weeks until Month 3 and then every 3 months thereafter. A fasting lipid profile was collected at baseline, every 3 months until Month 12 and then at Months 18 and 24. Episodes of neutropenia, lymphopenia and abnormalities of liver function tests (particularly, elevated serum transaminases) were an AE of special interest as this was an identified risk with TOF.
- Screening tests for tuberculosis (Chest x-ray and QuantiFERON Gold testing; or PPD skin testing in countries without QuantiFERON Gold testing) were taken at baseline, but not routinely collected thereafter.
- Vital signs such as blood pressure, heart rate and subject weight were performed at each scheduled study visit.
- ECG was taken at baseline and at the month 12 and 24 visits.

AEs were summarised by the MedDRA classification using the System Organ Class (SOC) and Preferred Term (PT) nomenclature.

The final 2 year report for Study A3921044 has been previously evaluated in detail and that information is included in the current PI. As such, the safety data from that trial will not be considered separately in this report. Nonetheless, safety information from Study A3921044 contributes to the integrated safety population.

Other studies

Other efficacy studies

In addition to Studies A3921044 and A3921069, another four Phase III studies (A3921032, A3921045, A3921046 and A3921064) and two open label, LTE studies (A3921024 [ongoing] and A3921041 [completed] have contributed safety data to the integrated safety dataset included in this submission. Two of the Phase III trials (A3921045 and A3921069) were TOF monotherapy studies, whereas all of the other four Phase III studies involved the addition of TOF to background DMARD, mainly MTX. All but one of the trials included 2 dose regimens of TOF; 5 mg twice daily and 10 mg twice daily. The TGA approved dose is 5 mg twice daily, but for completeness of the safety data review, the TOF 10 mg twice-daily regimen is considered in this review. Study A3921024 is a global located trial, whereas Study A3921041 was only conducted in Japan. Study A3921041 initiated all subjects on TOF 5 mg twice daily and subjects from China in Study A3921024 also did the same. As a result, there is a geographically skewed distribution of TOF 5 mg therapy in Asian subjects overall, which appears to be an at risk population for certain AEs including interstitial lung disease and specific opportunistic infections like *Pneumocystis jirovecii* pneumonia (PJP).

Studies with evaluable safety data: dose finding and pharmacology

The integrated safety population in this submission also included safety information from two Phase 1 studies (A3921030 and A3921152) and nine Phase II studies (A3921019, A3921025, A3921035, A3921039, A3921040, A3921068, A3921073, A3921109 and A3921129).

Studies evaluable for safety only

Nil in addition to Study A3921237.

Overview of Safety Data Presentations

In this submission, the sponsor presented safety information in 3 main populations. Firstly, the complete 2 year dataset for Study A3921069 was presented in isolation. Secondly, the sponsor pooled safety data from the controlled periods (0 to 3 months, or 0 to 6 months) in all 6 of the Phase III studies to examine certain safety endpoints for example risk of infection and various abnormal laboratory results like hyperlipidaemia. Finally, the total integrated safety dataset, which the sponsor calls the 'P123LTE' population, was provided for certain safety outcomes if changes to the current PI are proposed.

Patient exposure

Table 3 presents the total number of subjects with RA who have received at least 1 dose of TOF in clinical trial program, and the same table displays the drug exposure (mean and total) to TOF across the different nominated safety populations such as all 6 Phase III studies combined, Study A3921069 in isolation, the 2 LTE trials combined and finally, the total integrated safety dataset, which the sponsor calls the 'P123LTE' population.

Table 3: TOF Exposure in Main Safety Populations

Population	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			All Tofacitinib Doses		
	Subjects (n)	Total Exposure (PY)	Mean Duration (Year)	Subjects (n)	Total Exposure (PY)	Mean Duration (Year)	Subjects (n)	Total Exposure (PY)	Mean Duration (Year)
Phase 3 RCTs	1589	1743.9	1.10	1611	1799.5	1.12	3800	3941.5	1.04
1069	373	611.09	1.64	397	651.17	1.64	770	1262.26	1.64
LTE									
Average Dose	1471	5278.0	3.55	3396	9647.8	2.81	4867	14925.8	3.07
P123LTE									
Average Dose	2239	6870.2	3.07	3955	12535.7	3.17	6194	19405.8	3.13
Constant Dose	2342	3623.4	1.55	2814	6701.8	2.38	NC	NC	NC

BID=twice daily, LTE=long-term extension, NC=not calculated, PY=patient-year, RA=rheumatoid arthritis, RCT=randomised controlled trial

As a comprehensive analysis of the 24 month safety dataset for Study A3921069 is a focus of this submission, the number of subjects exposed to study drug (either dose of TOF or MTX) over time in this particular trial is presented in Table 4. In this pivotal trial, most patients (> 60% in the MTX group and almost three quarters in each of the TOF arms) took their allocated study treatment for at least 18 months in Study A3921069.

Table 4: Number of Subjects and Drug Exposure by Treatment Group in Study A3920169

	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Methotrexate
Number of Subjects	373	397	186
Duration Category (Month)			
≤1 month	9	6	7
>1 to ≤ 3 month	16	14	10
>3 to ≤6 month	18	21	19
>6 to ≤ 12 month	25	32	18
>12 to ≤ 18 month	27	33	19
>18 month	278	291	113

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Integrated safety analyses

No new information provided in this submission.

Pivotal and/or main efficacy studies

In Study A3921069, subjects treated with TOF showed a slight median increase from baseline in serum ALT of 2 to 3 IU/L, which peaked at 6 months and remained stable thereafter up to 24 months. Subjects treated with MTX showed a median increase from baseline of 4 IU/L at month 6, which stabilised thereafter. Changes of similar magnitude were observed for serum AST in all 3 treatment groups. The median changes from baseline in serum total bilirubin through to 24 months were minimal in all 3 treatment groups.

In Study A3921069, the majority of subjects in all 3 treatment groups remained within normal limits for serum transaminases (ALT/AST) and bilirubin. Most subjects with abnormal liver function results were in the ≥ 1 x ULN category, and the affected subject proportions were as common in the MTX and TOF groups – refer to Table 5. The most notable difference between treatment groups was observed for the percentage of subjects with ALT or AST ≥ 3 x ULN, which was an abnormality seen at least twice as frequently with MTX compared to TOF.

Table 5: Proportion of Subjects with Abnormal Liver Function Tests in Study A3921069

Number (%) Subjects	Tofacitinib 5 mg BID (N=368)	Tofacitinib 10 mg BID (N=396)	MTX (N=184)
ALT			
≥1×ULN	132 (35.9)	150 (37.9)	79 (42.9)
≥2×ULN	19 (5.2)	40 (10.1)	24 (13.0)
≥3×ULN	11 (3.0)	12 (3.0)	13 (7.1)
AST			
≥1×ULN	121 (32.9)	143 (36.1)	56 (30.4)
≥2×ULN	14 (3.8)	22 (5.6)	12 (6.5)
≥3×ULN	6 (1.6)	6 (1.5)	6 (3.3)
Total Bilirubin			
≥1×ULN	18 (4.9)	26 (6.6)	8 (4.3)
≥2×ULN	1 (<1.0)	3 (<1.0)	0
≥3×ULN	0	0	0

N refers to the sample size at the start of the period indicated for this table, NOT the BASELINE.
ALT=alanine transaminase, AST=aspartate transaminase, BID=twice daily, MTX=methotrexate, N=number of evaluable subjects, ULN=upper limit of normal.

In Study A3921069, 12 (3.2%) subjects in the TOF 5 mg group, 13 (3.3%) patients in the TOF 10 mg arm and 13 subjects (7%) in the MTX group met the protocol criteria for further intensive monitoring (that is elevated serum transaminases on 2 consecutive readings). Two subjects in the TOF 10 mg group and 1 subject in the MTX arm had to permanently discontinue treatment due to persistent abnormalities of liver function tests. In addition, 2 subjects (both treated with TOF 10 mg therapy) met the initial screening process of potential Hy's Law cases (that is serum ALT or AST ≥ 3 x ULN and bilirubin ≥ 2 x ULN). However, 1 case was subsequently dismissed because she did not meet the biochemical definition. This patient had an increase in serum ALP > 2 x ULN in conjunction with raised serum transaminases but normal serum bilirubin. The other case was also subsequently dismissed upon sponsor review. Another patient with a history of poorly controlled hypertension and biliary lithiasis recorded an SAE of biliary colic on study day 478 (confirmed on ultrasound on study Day 480), which resolved within 2 weeks of onset.

Other studies

No new information provided in this submission.

Renal function and renal toxicity

Integrated safety analyses

In the long term integrated dataset, the proportion of subjects who showed 2 consecutive increases in serum creatinine levels > 50% above their baseline value (that is the protocol specified TOF discontinuation criteria) was 2.4%. The 2.4% event figure is slightly higher than the 2% figure quoted in the current PI, so the sponsor has proposed an amendment to the PI to reflect the slightly higher observed incidence of significant change in renal function with long term TOF therapy.

Pivotal and/or main efficacy studies

In Study A3921069, the baseline mean serum creatinine levels in the 3 treatment groups were similar at 64.55 to 65.43 µmol/L. Up to 24 months, TOF treatment (either dose) produced a mean increase from baseline of 8.84 µmol/L in serum creatinine (evident from 6 months and stable thereafter) compared to a mean increase of 4.42 µmol/L in the MTX group.

In Study A3920169, the proportions of patients with raised serum creatinine (both ≥ 33% and > 50% of the average of the screening and baseline values; on at least 2 consecutive visits) were greater in the TOF arms than the MTX group. The proportion of patients who

developed raised serum creatinine ≥ 33% of their baseline/screening value (which was the protocol defined threshold for intensive monitoring) was 9.9% (37 out of 373) in the TOF 5 mg group, 9.5% (38 out of 399) in the TOF 10 mg arm and 2.7% (5 out of 186) in the MTX group. The percentage of subjects who recorded raised serum creatinine > 50% of their baseline/screening value (which was the protocol defined threshold for drug discontinuation) was 1.6% (6 out of 373) in the TOF 5 mg group, 2.5% (10 out of 399) in the TOF 10 mg arm and zero in the MTX group.

Other studies

No new information.

Other clinical chemistry

Integrated safety analyses

No new information.

Pivotal and/or main efficacy studies

Over 24 months of observation in Study A3921069 (without regard to baseline values), the percentage of subjects who experienced a > 2 fold increase in serum CPK reading was significantly higher with TOF therapy (in a dose related manner) compared to MTX. Overall, 12.5% (46 out of 368) of subjects in the TOF 5 mg group, 22.2% (88 out of 396) of patients in the TOF 10 mg arm and 3.8% (7 out of 184) of subjects in the MTX group developed 2 fold increases in serum CPK levels. One subject discontinued from Study A3921069 because if increased CPK. A 29 year old male in the TOF 5 mg group permanently discontinued from the trial because of rhabdomyolysis with the peak serum CPK value being 3680 U/L on study day 450. No other patients recorded rhabdomyolysis in Study A3921069. No other significant abnormalities of clinical chemistry were observed.

Other studies

No new information.

Haematology and haematological toxicity

Integrated safety analyses

With the addition of data from Study A3921069 and the latest data cut-off date of 31 March 2015, the sponsor proposes updating the rates of lymphopenia in the Adverse Effects section of the PI from the current 0.21% to 0.23% for patients treated with TOF in the controlled clinical studies, and from 0.31% to 1.3% of patients in the long term safety population.

Pivotal and/or main efficacy studies

After 24 months of treatment in Study A3921069, the median decrease from baseline in absolute neutrophil counts was -1.17, -1.57 and -0.85 x 10^9 cells/L in the TOF 5 mg, TOF 10 mg and MTX groups, respectively. The study also demonstrated greater median decreases from baseline in total lymphocyte counts with TOF (5 and 10 mg therapy) compared to MTX over the 2 year period. The median change from baseline to last observation in total lymphocyte count was -0.33, -0.43 and -0.16 x 10^9 cells/L in the TOF 5 mg, TOF 10 mg and MTX groups, respectively. For all 3 groups, no significant mean changes over time in haemoglobin levels were observed.

As JAK2 is an important mediator of erythrocyte production, anaemia was a safety focus in Study A3921069. Overall, the proportion of patients who experienced severe (up to 3.5% incidence with MTX versus up to 1.4% with TOF) or potentially life threatening decreases in haemoglobin levels was low (< 1% of patients in any treatment group) at any time-point throughout Study A3921069. Table 6 summarises the proportions of patients with

decreased haemoglobin values (based on the OMERACT criteria) by visit and treatment group in Study A3921069.

Table 6: Proportion of subjects with decreased haemoglobin levels during Study A3921069

Visit[a]	Treatment	N	Mild to Moderate n (%)	Severe n (%)	Potentially Life Threatening n (%)
Month 3	Tofacitinib 5 mg BID	352	23 (6.5)	2 (<1.0)	2 (<1.0)
	Tofacitinib 10 mg BID	382	30 (7.9)	2 (<1.0)	0
	Methotrexate	173	20 (11.6)	2 (1.2)	0
Month 6	Tofacitinib 5 mg BID	339	23 (6.8)	2 (<1.0)	0
	Tofacitinib 10 mg BID	365	25 (6.8)	4 (1.1)	0
	Methotrexate	158	18 (11.4)	1 (<1.0)	1 (<1.0)
Month 9	Tofacitinib 5 mg BID	326	25 (7.7)	0	2 (<1.0)
	Tofacitinib 10 mg BID	345	36 (10.4)	4 (1.2)	1 (<1.0)
	Methotrexate	140	12 (8.6)	0	0
Month 12	Tofacitinib 5 mg BID	311	26 (8.4)	3 (<1.0)	1 (<1.0)
	Tofacitinib 10 mg BID	328	32 (9.8)	0	0
	Methotrexate	131	16 (12.2)	2 (1.5)	0
Month 18	Tofacitinib 5 mg BID	279	23 (8.2)	4 (1.4)	0
	Tofacitinib 10 mg BID	291	34 (11.7)	3 (1.0)	1 (<1.0)
	Methotrexate	114	8 (7.0)	4 (3.5)	0
Month 24	Tofacitinib 5 mg BID	273	29 (10.6)	2 (<1.0)	1 (<1.0)
	Tofacitinib 10 mg BID	287	38 (13.2)	4 (1.4)	0
	Methotrexate	109	16 (14.7)	3 (2.8)	1 (<1.0)

Decreased hemoglobin from Baseline was defined using OMERACT[11] criteria as follows:
Mild or moderate: A decrease of ≥1 g/dL to ≤2 g/dL compared to Baseline.
Severe: A decrease of >2 g/dL to <3 g/dL compared to Baseline or an actual hemoglobin result of ≥7 g/dL, but <8 g/dL.
Potentially life-threatening: A decrease of ≥3 g/dL compared to Baseline or an actual hemoglobin result of ≤7 g/dL.
Abbreviations: BID = twice daily, N = number of patients, n = number of patients meeting prespecified criteria, OMERACT = Outcome Measures in Rheumatoid Arthritis Clinical Trials, MTX = methotrexate

The case incidence of mild (frequency of up to 3.5%) or moderate to severe neutropenia (incidence ≤ 1.8%) was relatively low and comparable between the low dose TOF and MTX groups throughout Study A3921069, but somewhat higher in a consistent pattern for the TOF 10 mg arm; refer to Table 7. However, only 1 patient developed potentially life threatening neutropenia during the 24 month trial and that subject was treated with TOF 5 mg therapy (occurred at Month 15).

Table 7: Proportion of Subjects recording Neutropenia during Study A3921069

Visit	Treatment	N	Mild Neutropenia n (%)	Moderate to Severe Neutropenia n (%)	Potentially life-threatening n (%)
Baseline	Tofacitinib 5 mg BID	372	3 (<1.0)	1 (<1.0)	0
	Tofacitinib 10 mg BID	397	1 (<1.0)	0	0
	Methotrexate	186	1 (<1.0)	0	0
Month 3	Tofacitinib 5 mg BID	351	7 (2.0)	2 (<1.0)	0
	Tofacitinib 10 mg BID	382	15 (3.9)	4 (1.0)	0
	Methotrexate	173	2 (1.2)	1 (<1.0)	0
Month 6	Tofacitinib 5 mg BID	339	6 (1.8)	3 (<1.0)	0
	Tofacitinib 10 mg BID	364	10 (2.7)	4 (1.1)	0
	Methotrexate	158	4 (2.5)	0	0
Month 9	Tofacitinib 5 mg BID	325	4 (1.2)	3 (<1.0)	0
	Tofacitinib 10 mg BID	345	14 (4.1)	2 (<1.0)	0
	Methotrexate	140	3 (2.1)	0	0
Month 12	Tofacitinib 5 mg BID	310	6 (1.9)	3 (<1.0)	0
	Tofacitinib 10 mg BID	328	16 (4.9)	1 (<1.0)	0
	Methotrexate	130	1 (<1.0)	0	0
Month 15	Tofacitinib 5 mg BID	287	5 (1.7)	2 (<1.0)	1 (<1.0)
	Tofacitinib 10 mg BID	309	10 (3.2)	2 (<1.0)	0
	Methotrexate	127	2 (1.6)	0	0
Month 18	Tofacitinib 5 mg BID	278	5 (1.8)	3 (1.1)	0
	Tofacitinib 10 mg BID	291	11 (3.8)	1 (<1.0)	0
	Methotrexate	114	1 (<1.0)	2 (1.8)	0
Month 21	Tofacitinib 5 mg BID	271	5 (1.8)	2 (<1.0)	0
	Tofacitinib 10 mg BID	287	10 (3.5)	0	0
	Methotrexate	109	2 (1.8)	0	0
Month 24	Tofacitinib 5 mg BID	256	9 (3.5)	1 (<1.0)	0
	Tofacitinib 10 mg BID	278	12 (4.3)	5 (1.8)	0
	Methotrexate	102	1 (<1.0)	0	0

Mild neutropenia: ANC ≥1.5 to $<2\times10^3/\mu L$; moderate to severe neutropenia: ANC ≥0.5 to $<1.5\times10^3/\mu L$; life-threatening neutropenia: ANC $<0.5\times10^3/\mu L$.
Abbreviations: ANC = absolute neutrophil count, BID = twice daily, N = number of patients, n = number of patients with prespecified criteria, MTX = methotrexate

A total of 5 patients (3 in the TOF 5 mg group, and 1 each in the TOF 10 mg and MTX arms) developed thrombocytopenia (platelet count < 100 x 10^9/L) during Study A3921069. Only 1 subject in the TOF 5 mg group developed significant lymphopenia (< 0.5 x 10^9/L) which persisted on 2 sequential readings during the trial.

Other studies

No new information.

Lipid Profiles

Integrated safety analyses

No new information.

Pivotal and/or main efficacy studies

Treatment with TOF produces a significant, dose dependent increase in serum total cholesterol, which is evident by 3 months of therapy, plateaus at 6 months and remains stable thereafter up to 24 months of treatment follow-up. By 24 months, TOF 5 mg twice daily results in a mean 17.4% increase from baseline in total cholesterol and TOF 10 mg twice daily causes a mean 20.7% increase from baseline. Similar results with TOF were observed for low density lipoprotein levels and serum triglyceride levels. No significant mean changes in any lipid parameters over time are seen with MTX therapy.

Other studies

Changes in lipid parameters from baseline through to the end of the controlled trial periods (up to 24 months) in the Phase III studies confirms that significant, dose dependent increases in serum total cholesterol, LDL cholesterol and HDL cholesterol with TOF remain stable after 3 to 6 months of drug initiation. The current PI contains data on the impact of TOF upon lipid profiles up to 12 months in the controlled trials, so the update on this issue is appropriate. Table 23 shows the mean percentage change (increase) from baseline to 24 months in LDL cholesterol in the combined Phase III dataset.

Table 8: Mean percentage change from Baseline to 24 Months in LDL cholesterol in the combined Phase III Trial Population

Period	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		Tofacitinib All Doses		Placebo	
	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)	N	Mean Change (SD)
Month 1	1152	11.13 (22.91)	1151	15.79 (25.81)	2303	13.46 (24.51)	637	-0.12 (17.09)
Month 3	1454	13.71 (24.87)	1485	18.20 (27.24)	2939	15.98 (26.18)	611	0.26 (20.18)
Month 6	1587	14.10 (26.20)	1595	18.16 (28.74)	3182	16.14 (27.57)	171	-2.43 (17.29)
Month 9	1182	14.29 (28.44)	1198	18.82 (31.95)	2380	16.57 (30.34)	NA	NA
Month 12	1132	15.02 (27.68)	1124	20.48 (32.55)	2256	17.74 (30.32)	NA	NA
Month 18	561	15.98 (28.31)	577	18.47 (33.33)	1138	17.24 (30.97)	NA	NA
Month 24	507	16.34 (29.06)	530	19.29 (34.79)	1037	17.85 (32.13)	NA	NA

The treatments represent the initial randomised study drug.
Includes Protocols - A3921032, A3921044 (2 year data), A3921045, A3921046, A3921064, A3921069 (2 year data)
BID=twice daily, CI=confidence interval, LDL-c=low-density lipoprotein cholesterol, NA=not applicable, P3=phase 3, RCT=randomised controlled trial, SD=standard deviation

Electrocardiograph findings and cardiovascular safety

Integrated safety analyses

No new information.

Pivotal and/or main efficacy studies

Electrocardiograms (ECG) were obtained for all patients at the screening, Months 12 and 24. At screening, the percentage of patients with ECG abnormalities was small and similar (incidence ranging from 3.9 to 4.4%) across the 3 treatment groups. At Months 12 and 24, the percentage of patients with an increase from baseline in QT intervals of 30 to 60 msec and an increase from baseline of ≥ 60 msec were numerically similar (incidences ranging from 0 to 0.3%) in all treatment groups.

Other studies

No new information.

Vital signs and clinical examination findings

Integrated safety analyses

No new information.

Pivotal and/or main efficacy studies

In Study A3921069, the mean increase from baseline in body mass index was numerically greater in the 2 TOF groups than in the MTX arm at all time-points over 2 years, but the overall changes were small in all 3 treatment groups (< 1.5 kg/m^2 at all time-points). Minimal changes in heart rate were observed during the 2 year treatment period in Study A3921069, which were comparable between the 3 treatment groups.

Although there were no significant mean changes in systolic and diastolic blood pressure over time with any treatment in Study A3921069, a greater proportion of subjects reported hypertension related AEs (as coded for by the Standardised MedDRA Query) in the TOF 5 mg (9.4%; 35 out of 373) and TOF 10 mg (10.3%; 41 out of 397) groups compared to the MTX arm (4.3%; 8/186). One subject in the TOF 10 mg group permanently discontinued due to hypertension.

Other studies

No new information.

Post marketing data

As of November 2015, the sponsor estimates that 34,000 PY of drug exposure with 3 years of global availability (based on sales data) has occurred. However, the Australian post-marketing experience is limited with sales of 4384 packs of 14 tablets recorded up to 31 July 2015 since the launch of TOF in Australia in March 2015. No specific post-marketing report was provided in this submission.

Evaluator's conclusions on safety

In this submission for extension of treatment indication in patients with active RA, the sponsor has provided an update to the overall safety database for TOF (as of the data cut-off date of 31 March 2015), as well as new Phase II study (A3921237) which evaluated the effects of TOF 5 mg twice daily on the zoster vaccine immune response in patients with RA.

The total clinical safety dataset for the use of TOF (any dose) in adult patients with active RA consists of 19,406 PY of drug exposure observed in 6,194 patients. Of the treated subjects, 3,470 have received treatment for > 2 years, 1,443 subjects have received therapy for > 4 years and 345 patients have been exposed for > 6 years. In terms of the approved TOF regimen of 5 mg twice daily, 1,589 patients have been exposed for a total of 1743.9 PY in the Phase III controlled studies and in the LTE population, 1,471 patients have taken TOF for a mean duration of 3.5 years, which represents a total drug exposure at the registered dose of 5278 PY. About 80% of patients in the RA dataset have received concurrent conventional DMARD (usually low dose weekly MTX), more than 70% were taking concomitant NSAID, and approximately half were taking concurrent low dose oral CS. Overall, there is a sufficient volume of data to make a meaningful assessment of TOF safety (5 mg twice daily) for up to 7 years of treatment in adult patients with active RA.

Up to 24 months in Study A3921069, TOF 5 mg twice daily therapy + low dose weekly MTX showed a similar incidence of overall AEs, SAEs and AEs resulting in permanent treatment discontinuation compared to PBO tablets + continued MTX. However, some types of AEs occurred at a higher incidence in the TOF group (versus MTX) such as increased blood CPK levels, bronchitis and hypertension. In contrast, nausea and diarrhoea were more common with MTX versus MTX. Infection was the most common AE recognised with TOF and these occurred at a higher frequency in the TOF treatment groups versus control during the true PBO controlled treatment periods (3 to 6 months for most Phase III trials). The majority of infections were mild in severity, self-limiting, and were predominately either nasopharyngitis or URTI. The use of concurrent MTX did not appear to increase the overall risk of AEs, including infection related AEs. SAEs including serious infection related events were reported in a low proportion of TOF treated patients (< 3.0 serious infections per 100 PY of exposure). Some patients treated with TOF 10 mg twice daily developed reactivation of latent TB. However, there was an increased risk of herpes virus infections with any dose of TOF. This finding may be expected given the role of multiple cytokines in protective immunity. The majority of herpetic infections were

rated as mild or moderate in severity, responded to standard treatment and did not result in permanent discontinuation from TOF, but there reports of disseminated herpes zoster.

Hypertension is an uncommon type of AE reported at a slightly higher incidence in patients receiving TOF (with no dose response relationship) compared to PBO therapy. Most hypertension related AEs were rated as mild or moderate in severity and did not result in discontinuation from TOF.

Cases of gastrointestinal perforation are a safety concern with TOF therapy, but the integrated dataset revealed a relatively low incidence of such events (< 0.07 per 100 PY) with TOF 5 mg twice daily therapy. Four treatment emergent deaths were reported in Study A3921069 (all in TOF treated subjects) and a total of 90 deaths have been reported in patients with RA in the long term safety population. The rate of malignancies observed in Study A3921069 is within expectations of the treatment population and the types of cancer observed did not identify any specific new safety signals with TOF. There were also several MACE reports in Study A3921069, but overall these were within expectations for the selected treatment population. Nonetheless, longer periods of treatment follow-up are required to inform about these potential safety concerns (malignancy and MACE).

Neutropenia and lymphopenia are recognised safety concerns with TOF therapy and the issue was identified in the original TGA submission. In the short term period (first 3 to 6 months) of the Phase III studies, the overall incidence of neutropenia and lymphopenia was higher in both TOF (5 and 10 mg twice daily) treatment groups compared with PBO. There were occasional cases of severe neutropenia or lymphopenia observed in both TOF treatment groups, which required treatment discontinuation. Over long term follow-up, the incidence of lymphopenia was only 1.3% with TOF. The majority of neutropenic and lymphopenic episodes were transient, and not associated with infection related AEs, but there is an association between severe lymphopenia and the incidence of treated and serious infection.

The total safety dataset also identified 4 other abnormalities of laboratory values which occurred at a numerically higher frequency in the TOF treatment cohorts compared with PBO or control populations. Elevations in hepatic transaminases, cases of raised CPK levels, increased serum creatinine levels and hyperlipidaemia have been associated with TOF. None of these abnormalities appear to display a dose response relationship with TOF. In general, patients who developed an increase in laboratory tests had changes of mild to moderate severity, which were mainly transient in nature (apart from the impact upon lipids) and without associated clinical sequelae. There are occasional permanent discontinuations from TOF because of persistent and/or severe abnormal laboratory results.

Study A3921237 demonstrated that in subjects aged at least 50 years with active RA despite MTX, VZV specific IgG responses at 2, 6 and 12 weeks following zoster vaccination were similar in TOF + MTX treated and control subjects (continued MTX monotherapy) indicating similar vaccine induced humoral immune responses. In addition, T cell subset analyses following zoster vaccination were similar between the 2 treatment groups indicating similar vaccine induced cell-mediated immune responses. The incidence and type of clinical safety outcomes and laboratory test abnormalities observed in Study A3921237 were consistent with the known safety profile of TOF. There were no SAEs observed in the control arm, but 3 subjects treated with TOF permanently discontinued from the trial due to 4 SAEs, all of which resolved by 2 weeks off therapy. In general, zoster vaccination appeared safe in all subjects except 1 patient who lacked pre-existing exposure to varicella infection. Cutaneous dissemination of vaccine strain VZV occurred in one TOF treated subject who recovered without sequelae on anti-viral therapy.

Because TOF is an oral targeted synthetic DMARD (in contrast to biologic DMARD therapy administered by intravenous infusion or subcutaneous injection) it is neither expected nor observed to produce immunogenicity or an increased incidence of allergic skin reactions.

In summary, the safety data indicates that TOF 5 mg twice daily has an acceptable overall safety profile up to 7 years of therapy in the treatment of adult patients with moderately to severely active RA. There is limited long term safety data to assess the risk of some types of AEs such as malignancy and MACE, which will require additional longitudinal safety follow-up. There are some significant identified safety concerns including the risk of overall infection, opportunistic infection (mainly herpes viral infection and TB), neutropenia, lymphopenia, abnormal liver function tests and dyslipidaemia. These safety concerns are consistent with the known safety profile of TOF in adult patients with RA. Ongoing pharmacovigilance will be required for the continued registration of TOF in the treatment of patients with RA. This would include vigilance for opportunistic infections, MACE and malignancy (particularly, non-melanoma skin cancers and lymphoma).

First round benefit-risk assessment

First round assessment of benefits

In this submission requesting an extension of treatment indication, the benefits of TOF 5 mg twice daily (with or without concomitant MTX) in adult patients with active RA are:

- TOF + MTX versus PBO + MTX results in statistically less worsening of structural progression (as measured by mean changes from baseline in mTSS) over 6 and 12 months when sensitivity and patient subset analyses (mostly, post hoc analyses) are applied to the x-ray dataset of Study A3921044. However, the primary x-ray analysis did not support a robust finding in favour of TOF therapy in a predominantly second line treatment population with established RA. Trial design and unexpectedly low rates of x-ray progression in the control group may have contributed to the non-statistical finding with the primary analysis.
- TOF therapy (versus MTX) is associated with a lower rate of structural disease progression at months 6, 12 and 24 months of treatment in a RA population with early disease (median < 12 months duration) who are mainly naive to DMARD therapy (Study A3921069), however, this is not the current approved treatment population for TOF in Australia and the sponsor is not requesting a change to the recommended patient treatment group.
- X-ray benefits with TOF versus PBO in Study A3921044 were observed in a treatment response enriched population (that is autoantibody positive subjects with established joint erosions and elevated CRP values at baseline). However, the generalisability of this finding to the Australian clinical practice setting is limited and has not been included in the sponsor proposed x-ray indication wording or PI.
- The magnitude and clinical relevance of the potential x-ray benefits with TOF versus alternative treatment options in adult patients with active RA is unclear and cannot be quantified with scientific rigor from the current dataset.
- Improvement in the signs and symptoms of RA (as per the ACR clinical response criteria), which appear to be maintained to at least 2 years of treatment in the two pivotal Phase III studies (A3921044 and A3921069).
- Persistence of clinical efficacy response for up to 7 years in the subgroup of patients who are responding to and tolerating TOF 5 mg twice daily therapy (as seen in the LTE Studies A3921024 and A3921041). The volume and recorded outcomes of the extended TOF treatment cohort is a relative strength of the current dataset.

- Correlation between improvements in RAMRIS erosion scores on MRI, and mTSS and ES on Plain x-ray at 6 months with TOF therapy (Study A3921068), which supports the plausibility of TOF exerting a possible structural modification effect (preliminary data only).
- Study A3921237 demonstrated that in subjects aged at least 50 years with active RA despite MTX, VZV specific IgG responses at 2, 6 and 12 weeks following zoster vaccination were similar in TOF + MTX treated and control subjects (continued MTX monotherapy) indicating similar vaccine induced humoral immune responses. In addition, T cell subset analyses following zoster vaccination were similar between the 2 treatment groups indicating similar vaccine induced cell mediated immune responses.
- Convenient mode of administration (oral ingestion) with an acceptable dosing schedule (twice daily administration) versus subcutaneous injection for a variety of other DMARD therapies.

First round assessment of risks

The risks of TOF in the proposed usage include:

- Increased incidence of overall infection compared to PBO, which are usually minor in severity (in particular, URTI and nasopharyngitis), but there is also an increased risk of serious infection with TOF.
- Increased risk of pneumonia (including compared to MTX) and various types of herpes infection (in particular, herpes zoster infection) with TOF.
- Increased risk of drug induced neutropenia and lymphopenia compared to PBO.
- Risk of precipitation of gastrointestinal perforation (mainly seen with the higher non-approved dose of TOF; 10 mg twice daily).
- Increased frequency of raised serum transaminases and atherogenic serum lipid profiles compared to PBO.
- Potential increased risk of malignancy and MACE requiring long term surveillance; not evident in the current safety dataset.
- Higher rates of hypertension with TOF versus control therapy, which are usually non-severe in nature and rarely leads to permanent treatment discontinuation.
- Increased rates of raised serum CPK values and occasional reports of rhabdomyolysis resulting in permanent treatment discontinuation from TOF.
- Potential for drug induced interstitial lung disease and reduction in renal function with TOF.
- TOF has not been studied in patients < 18 years of age, in subjects with significant organ dysfunction (including renal, hepatic or cardiac failure), those at risk of reactivated latent tuberculosis (requiring meticulous screening at baseline) and in pregnant or lactating women.
- TOF has not been studied and should not be used in combination with biologic DMARD therapy in patients with RA.

First round assessment of benefit-risk balance

The overall benefit-risk balance of TOF, with or without combination non-biologic DMARD (mainly, weekly low dose oral MTX) in adult patients with moderately to severely active RA, who have had an inadequate response to or intolerant of at least 1 DMARD, with

respect to inhibition of structural progression associated with RA is unclear. The claim of radiographic benefit in RA is an add-on claim to an overall treatment indication, which already includes improvement in the symptoms and signs as well improving physical function. Several biologic therapies approved in Australia for the treatment of RA also include a claim of radiographic benefit.

TOF is a small molecule drug that selectively inhibits JAK1 and JAK3, thereby blocking the effects of various pro-inflammatory cytokines. In this submission, TOF has been evaluated in a large clinical program, which complied with CHMP guidelines for evaluation of treatment in RA. The clinical studies have evaluated an adequate number of subjects in the target patient population and demonstrated that TOF 5 mg twice daily is an effective in the treatment of active RA. The complete radiographic dataset questionably suggests superior inhibition of x-ray progression in the currently approved treatment population, but superiority of this x-ray data has been observed in various sensitivity and patient subgroup analyses, many of which were not pre-specified in the statistical testing for the one true pivotal trial that recruited patients consistent with the approved treatment indication (that is Study A3921044).

The safety profile of TOF observed in the extended clinical safety dataset included in this submission is largely consistent with that known for TOF, based on the original TGA submission. The recognised risks with TOF therapy include an increased risk of infection and changes in certain laboratory parameters, in particular, decreases in neutrophil count and increases in hepatic transaminases and serum lipids. The risk profile of TOF is based on a total of 1589 TOF 5 mg twice daily treated patients with RA involved in the Phase III studies, as well as additional safety information collected from > 6000 patients treated with any dose of TOF in the all exposure population.

In the RA trials, there was an increased incidence in overall infections in the 2 TOF dose groups compared to PBO. The majority of reported infections were mild or moderate, upper respiratory tract infections. Herpes related infections were also more frequent with TOF compared to PBO. However, very serious opportunistic infections like TB were reported with TOF.

Neutropenia was much more frequently observed with TOF than PBO, but most cases were of mild severity (CTCAE Grade 1-2), transient and reversible. More severe neutropenia (CTCAE Grade 3-4) was also observed with TOF, but were rarely associated with serious infection. There was also an increased incidence of mild-moderate hepatic transaminase elevations, increased blood CPK levels and dyslipidaemia with TOF versus PBO. Significant changes in laboratory parameters associated with TOF were generally managed by dose interruptions.

Malignancy represents a theoretical risk with any immunosuppressive therapy, but there is limited evidence that TOF confers an increased risk for certain types of malignancy such as non-melanoma skin cancers and lymphoma in the current dataset.

First round recommendation regarding authorisation

The evaluator does not recommend acceptance of the sponsor's request for the extension of TOF registration to include the add-on claim of radiographic benefit in for the treatment of moderately to severely active RA in adult patients who have failed to respond to or are intolerant of at least 1 DMARD. There is only one pivotal trial in the current radiographic dataset (Study A3921044), which has rigorously examined for joint structural progression in the treatment population that reflects the approved indication for TOF in Australia. The evaluator recommends the sponsor be approved to add the x-ray data (as listed in the proposed PI), but no change to the treatment indication wording is recommended. The current submission provides unclear evidence that TOF 5 mg twice daily is effective in slowing the progression of structural joint damage in RA, but the data does not meet

rigorous and robust scientific standards such as being statistically significant on the primary pre-specified analysis of the FAS.

The evaluator recommends that the sponsor proposed claim of durability in clinical efficacy response and the various safety updates be included in the updated PI. No significant deficiencies or inaccuracies of that information is proposed in the new PI and all statements have been justified in this submission, except for the proposed changes to the malignancy and interstitial lung disease sections of the PI (subject to another TGA process of assessment).

Should approval of the sponsor's proposed extension of treatment indication for TOF in active RA be granted, the evaluator also recommends that approval be subject to:

- Satisfactory response to the questions in this report,
- Regular periodic safety update reports, and
- When available, the sponsor provides the TGA with the final clinical study report for the LTE Study A3921024.

Clinical questions

Pharmacokinetics

Nil

Pharmacodynamics

Nil

Efficacy

Question 1

In the pivotal Phase III Study A3921069, the control treatment arm was assigned weekly low dose methotrexate. The clinical study report did not provide information on the dose (including the proportion of subjects who received dose split regimens as specified in the protocol) as well as the route of administration of methotrexate after 3 months to allow evaluation of the adequacy of comparator treatment. Recent expert opinion has identified suboptimal methotrexate therapy (dose and route of administration) as a source of biasing findings in favour of biologic therapies in RA clinical trials. Could the sponsor comment on the adequacy of therapy in the control arm of Study A3921069 (over the entire 24 months) as a potential source of efficacy bias?[5]

Question 2

Could the sponsor provide information about the dose and duration of preceding methotrexate use, as well as any information regarding the dose, persistence and route of concomitant methotrexate use during the pivotal radiographic Study A3921044?

Question 3

In this submission, the 24 month x-ray dataset of Study A3921044 had various sensitivity and subgroup analyses applied, many of which were post-hoc in nature, which suggested a potential treatment benefit with tofacitinib in reducing the rate of x-ray progression in RA. Can the sponsor comment on the scientific validity and robustness of such findings (in

[5] Durán J, et al. Methotrexate dosage as a source of bias in biological trials in rheumatoid arthritis: a systematic review. *Ann Rheum Dis.* 75: 1595-1598 (2016).

particular, the use of post-hoc analyses) with respect to a claim of inhibition of structural damage progression with tofacitinib?

Question 4

Could the sponsor comment on the clinical relevance of the magnitude of treatment related x-ray differences between tofacitinib and control therapy in both pivotal studies included in this submission? In particular, can the sponsor provide scientific validation of the relationship between radiographic progression and clinical outcomes, and what is the minimal clinically important difference in x-ray scores over time?

Safety

Question 5

In the long term safety all exposure population, the incidence rate of all-cause mortality with tofacitinib 5 mg twice daily was more than double that observed for tofacitinib 10 mg twice daily therapy (RMP). Could the sponsor comment on the relevance of this observation and provide a potential explanation?

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of TOF 5 mg twice daily therapy for the treatment of adult patients with active RA in the proposed usage are unchanged to those identified in this report. The current supporting radiographic dataset is limited to a single pivotal Phase III study (A3921044) which was well conducted and this trial failed to demonstrate a robust and clinically meaningful x-ray benefit with TOF 5 mg twice daily therapy versus control on the primary pre-specified analysis. The null x-ray result may have been impacted by factors such as an unexpected low rate of x-ray progression in the control arm making it difficult to demonstrate a clear treatment related benefit with low dose TOF, but this has been recognised in several x-ray studies in patients with active RA in the last 7 years, and is also a feature (that is less x-ray progression over time) seen in contemporary Australian whereby patients are generally treated earlier and more effectively. Because of the limitations of post hoc analyses, the x-ray response data provided in the response to questions does not support a robust scientific claim of additional benefit with TOF 5 mg twice daily therapy with respect to inhibition of the progression of structural damage. There are features of Study A3921044, which limit the external validity of its findings. In particular, the screen failure rate was 38% and approximately one third of all subjects (at a similar incidence in the 3 treatment groups) appeared to receive an insufficient prior dose of MTX (that is ≤ 12.5 mg/week) for unclear reasons, before proceeding to second line therapy (with either dose of TOF or continued MTX). Similarly, approximately one third of the PBO treated continued with sub-optimal MTX dosing during Study A3921044. Post hoc analysis of the x-ray data in a high risk patient population was statistically in favour of TOF 5 mg therapy versus PBO, but this observation has the caveat of reducing the generalisability of the observation. To further complicate the assessment for a claim of x-ray benefit with TOF 5 mg twice daily therapy, there is a paucity of published scientific data to define the minimally clinically important difference in x-ray scores over time.

Study A3921069 provides supportive data to the claim of x-ray benefit with TOF 5 mg twice daily, but the main limitation of interpreting this patient dataset is that it examined predominately treatment naïve patients with active RA. This patient group is inconsistent with the current approved treatment indication for TOF 5 mg twice daily therapy (that is second or subsequent line of treatment option) and the sponsor is not requesting alteration to the line of therapy initiation with this submission. In addition, approximately 40% of subjects (75 out of 186) in the MTX arm of Study A3921069 did not reach a weekly MTX dose of 17.5 to 20 mg/week for unclear reasons, which suggests a larger than expected cohort of comparator treatment subjects may have received sub-optimal treatment.

In conclusion, the x-ray benefit of TOF 5 mg twice daily treatment (using data obtained in Study A3921044 and A3921069) is unclear with respect to a broad group of patients with active RA and the clinical relevance of any statistically significant observations are unclear. On the current dataset, the evaluator does not recommend that the additional treatment indication claim of radiographic benefit with TOF 5 mg twice daily therapy be approved.

Second round assessment of risks

After consideration of the responses to the clinical questions (principally, Question 5), the risks of TOF are unchanged from those identified in this report. The increased incidence rate of all-cause mortality in the long term TOF 5 mg twice daily treated group of patients versus those who received TOF 10 mg twice daily remains within expectations for the RA population cohort, and the types of deaths recorded is also consistent with expectations. As such, this observation is unlikely to be of clinical significance and does not unfavourably impact upon the overall benefit: risk assessment for long term TOF 5 mg twice daily therapy.

Second round assessment of benefit-risk balance

After consideration of the responses to the clinical questions, there is no change to the opinion expressed. The overall benefit-risk balance of TOF 5 mg twice daily treatment in the proposed additional treatment indication claim of inhibition of the progression of structural damage in active RA is unclear. Clinically relevant, robust efficacy (with respect to x-ray benefit) has not been observed with TOF 5 mg twice daily therapy in the current approved RA patient population (that is second line treatment group). However, the durability of clinical response has been presented in the submission. Furthermore, the longer term safety dataset does not reveal any significant changes in the incidence and pattern of unfavourable effects over time and was consistent with the expected profile for TOF. The major risks with TOF therapy (versus PBO) include an increased risk of infection, raised serum transaminases, atherogenic lipid profiles, neutropenia and lymphopenia.

Second round recommendation regarding authorisation

The evaluator does not recommend acceptance of the sponsor's request for the extension of treatment indication of TOF 5 mg twice daily treatment to include a claim of radiographic benefit. There is only 1 pivotal trial in the x-ray dataset (Study A3921044), which has rigorously examined for joint structural progression in the approved treatment population and this reveals an unclear benefit with TOF 5 mg twice daily versus PBO (and continued low dose MTX), which is of uncertain clinical relevance. On the balance of scientific evidence and validity, the sponsor proposed add on treatment claim of inhibition of the progression of structural damage as measured by plain x-ray for TOF 5 mg twice daily is insufficiently acceptable. The sponsor proposed changes regarding durability of clinical response and updated safety data with TOF are acceptable for inclusion in the amended PI.

The evaluator recommends the continued registration of TOF 5 mg twice daily treatment for the treatment of active RA is subject to regular periodic safety update reports and when available, the sponsor provides the TGA with the final clinical study report for the long term Study A3921024.

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[6]

- The sponsor submitted an Australian specific RMP (version 2.0; 28 January 2016; data lock point 15 June 2015) in support of this application and did not provide a revision with the Section 31 response.
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised below.

Table 9: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Serious and other important infections	ü	ü*,^	ü	ü
	Decrease in neutrophil counts and neutropenia	ü	-	ü	ü
	Decrease in lymphocyte counts and lymphopenia	ü	ü^	ü	ü
	Decrease in haemoglobin levels and anaemia	ü	-	ü	ü
	Lipid elevations and hyperlipidaemia	ü	-	ü	ü

[6] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Nonmelanoma skin cancer	ü	ü*,^	ü	ü
	Transaminase elevation and potential for drug induced liver injury	ü	-	ü	ü
	Gastrointestinal perforation	ü	ü*	ü	ü
	Hypertension	ü	-	ü	-
	Creatine kinase increase	ü	-	ü	-
	Weight increase	ü	-	ü	-
Important potential risks	Malignancy (excl NMSC) including lymphoma	ü	ü*,^	ü	ü
	Cardiovascular risk	ü	ü*,^	ü	-
	Interstitial lung disease	ü	-	ü	-
	Progressive multifocal leukoencephalopathy	ü	ü*,^	-	-
	Rhabdomyolysis	ü	-	-	-
	Epstein-Barr Virus-related events	ü	-	ü	ü
	QT prolongation	ü	-	-	-
	Reduction in renal function	ü	-	ü	ü
Modified release formulation only	Gastrointestinal obstruction	ü	-	ü	-
Missing information	Effects on pregnancy and the foetus	ü	ü#	ü	ü
	Use in breastfeeding	ü	-	ü	-

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Effect on vaccination efficacy and the use of live/attenuated vaccines	ü	-	ü	ü
	Use in paediatric patients	ü	ü ^	ü	-
	Use in combination with biologic DMARDs, other biologic RA therapies, and immunosuppressants including B lymphocyte depleting agents	ü	-	ü	-
	Use in mild, moderate, or severe hepatic impairment	ü	-	ü	-
	Use in moderate or severe renal impairment	ü	-	ü	-
	Use in patients with evidence of hepatitis B or hepatitis C infection	ü	-	ü	-
	Use in patients with elevated transaminases	ü	-	ü	-
	Use in patients with malignancy	ü	-	ü	-

* = US-PASS registry; ^ = clinical trials; # = pregnancy registry

- Additional pharmacovigilance activities are ongoing for the safety concerns indicated in the table above.
- Additional risk minimisation, in the form of patient and healthcare professional education and a patient alert card have all been implemented to address the safety concerns indicated in the table above. The exception to this is that only prescriber education is being conducted for the important potential risks of 'Epstein-Barr virus related events' and 'reduction in renal function'.

New and outstanding recommendations from second round evaluation

- The sponsor has addressed the Round 1 RMP recommendations.

Proposed wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- Implement AUS-RMP version 2.0, 28 January 2016; data lock point 15 June 2015 submitted with PM-2015-04750-1-3 and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No new quality data were included in this submission.

Nonclinical

No new nonclinical data were included in this submission.

Clinical

The clinical evaluator has not recommended approval of the extension of indications for tofacitinib to include a claim of radiological benefit based on there being only one pivotal trial in the x-ray data set which rigorously examined for joint structural progression in the approved treatment population (Study A3921044). This study found an unclear benefit of tofacitinib 5 mg BD compared to PBO which was of uncertain clinical relevance. The evaluator considered the proposed changes to the PI regarding the durability of clinical response and updated safety data acceptable for inclusion in the PI.

The clinical evaluator has reviewed the following submitted data:

- Three Phase II studies (A3921068, A3921073 and A3921237)
- Two Phase III studies (2 year CSR for Studies A3921044 and A3921069)
  - Additional sensitivity and subgroup analyses of the data from Study A3921044
- Two open label, extension studies (one completed [A3921041] and one ongoing [A3921024])
- Updated safety data

Benefits noted by the evaluator included:

- TOF+MTX versus PBO+MTX resulted in statistically less worsening of structural progression (mean change in mTSS) over 6 and 12 months when sensitivity and patient subset analyses were applied to the x-ray dataset of Study A3921044.
- X-ray benefits with TOF versus PBO in Study A3921044 were observed in a treatment response enriched population.

- TOF therapy (versus MTX) is associated with a lower rate of structural disease progression at 6, 12 and 24 months of treatment in a RA population with early disease who are mainly naive to DMARD therapy (Study A3921069).
- Improvement in the signs and symptoms of RA appear to be maintained to at least 2 years of treatment (A3921044 and A3921069).
- Persistence of clinical efficacy response for up to 7 years in the subgroup of patients responding to TOF 5 mg BD therapy (LTE Studies A3921024 and A3921041).
- Correlation between improvements in Rheumatoid Arthritis Magnetic Resonance Imaging Score (RAMRIS) erosion scores on MRI, and mTSS and ES on Plain x-ray at 6 months with TOF therapy (Study A3921068)
- Similar vaccine induced humoral and cell mediated immune responses in subjects with active RA treated with TOF+MTX compared to MTX monotherapy (Study A3921237) at 2, 6 and 12 weeks following zoster vaccination.

Concerns noted by the evaluator included:

- The findings of the primary x-ray analysis of Study A3921044 were not supportive of an x-ray claim for TOF therapy in a predominantly second line treatment population with established RA.
- The magnitude and clinical relevance of the potential x-ray benefits with TOF versus alternative treatment options in adult patients with active RA is unclear.
- The generalisability of the x-ray results to the Australian clinical practice setting is limited.

Pharmacology

Study A3921024 is an ongoing, open label; LTE study in which lymphocyte subset cell counts were collected for a median duration of 5 years in TOF treated subjects. The long term data shows a persistent median reduction from baseline of CD4+ and CD8+ T cells of 28% and 27%, respectively. However, CD4+ and CD8+ cell counts recover to baseline values after 4 weeks of treatment discontinuation. Moreover, in contrast to the observed decrease in NK cell counts with 3 to 6 months of TOF treatment, long term therapy (2 to 5 years) shows a median increase of up to 73% in this lymphocyte subset. Treatment with TOF also results in dose dependent increases in CD19+ B cell counts, which show no further increases with prolonged TOF treatment. The study did not find evidence of an increased risk of serious infection in subjects with low CD4+/8+/NK cell counts or high B-cell counts. Therefore, specific monitoring of T cell subsets does not appear to be an effective risk minimisation strategy with TOF treatment. However, there is a correlation between the risk of serious infection and an absolute lymphocyte cell count of $< 0.5 \times 10^9$/L, which is already included in the current PI.

Efficacy

Study A3921044

Study A3921044 was a Phase III, randomised, double blind, placebo controlled trial of 2 years duration in which subjects were randomised to one of four parallel treatment sequences. The study allowed for early escape to rescue treatment for patients randomised to PBO with insufficient improvement at the 3 month visit.

The study included 797 patients, 18 years of age or older, with a diagnosis of active RA plus at least one of the following three features: at least three documented joint erosions on plain x-ray, or positive serology for anti-CCP antibodies or for RF. Subjects were

required to be on a stable weekly dose of MTX 15 to 25 mg, although MTX doses < 15 mg/week were allowed for patients intolerant of higher doses or recruited in countries where the higher dose would contravene local labelling recommendations. Overall, 67.6% (539) of patients completed 2 years of treatment. A total of 257 subjects (32.2%) discontinued from the trial, including 124 patients (15.6%) withdrawing due to AEs (91 patients had AEs considered to be treatment related).

There were 4 primary efficacy objectives, one of which was the assessment of slowing the progression of structural damage, which is the focus of this submission. The 4 primary efficacy objectives of Study A3921044 were evaluated in the initial TGA submission. A secondary objective of Study A3921044 was to evaluate the durability of various levels of ACR response, clinical remission (DAS28 score < 2.6) and low disease activity (DAS28 score < 3.2) with extended treatment follow-up.

The main radiographic outcome was the mean change from baseline in the mTSS. The plain x-rays were read in two campaigns. Campaign 1 involved the reading of x-rays up to 12 months. For Campaign 2, data up 24 months, all x-rays were re-read by 2 independent, blinded readers. The primary clinical endpoints were the rate of ACR20 response, mean change over time in the HAQ-DI score and other validated composite measures of disease activity and response in RA.

Approximately one third of all subjects appear to have received an insufficient dose of prior MTX (that is ≤ 12.5 mg/week) before proceeding to JAK inhibition. Detail on the relevant percentage of very low dose MTX recipients who recorded intolerability to MTX versus local prescribing restrictions was not provided. The PBO control arm did not receive maximal standard comparator treatment with MTX as their pre-existing regimen, for which they recorded inadequate response at baseline, was continued during the trial. In addition, the study had a screening failure rate of 38% (491 out of 1291). The potential sub-optimal preceding treatment reduces the generalisability of the study results.

The majority patients were female (85.1%; 678 out of 797) and either White (46.2%; 368 out of 797) or Asian (42.4%; 338 out of 797). The mean age of patients ranged from 52.0 years to 53.7 years (range 18 to 82 years). The treatment groups were similar with respect to baseline RA disease characteristics. The mean duration of RA was 8.8 to 9.5 years (range: 0.3 to 43.5 years). All patients were to have moderately to severely active RA with joint erosions or positive RF or positive anti-CCP antibodies at enrolment. These characteristics were meant to enrich the study population for they are associated with high risk of structural damage.

Results for the radiographic efficacy outcome

At baseline, the LS mean mTSS values were 31.26, 31.03 and 35.86 in the PBO (n = 139 subjects), TOF 5 mg (n = 287 subjects) and TOF 10 mg groups (n = 298 subjects), respectively. Treatment with TOF (5 mg or 10 mg) resulted in numerically less progression from baseline in the LS mean changes in mTSS scores compared to PBO extrapolated at months 6, 12 and 24, but this did not reach statistical significance for any pair wise comparison between active treatment with TOF and PBO.

The use of a significant amount of extrapolated x-ray data for the control group may have diluted the results of the x-ray dataset. Two additional post-hoc analyses, which focussed on the primary radiographic endpoint (LS mean change from baseline in mTSS at 6 months) were submitted. The first sensitivity analysis used the observed data for TOF and PBO treated subjects. Missing values at Month 6 were only extrapolated from 3 months for PBO treated subjects who advanced to TOF due to inadequate response. The second post-hoc sensitivity analysis was a random coefficients model that utilised all observed data between Months 3 and 12. PBO treated subjects who advanced to TOF were set to missing after advancement. This model used all observed data to estimate an average rate of change, which was then used to compute the six month changes from

baseline. Both sensitivity analyses showed a statistically significant reduction in the LS mean change from baseline to 6 months in mTSS (ranging from -0.33 to -0.42 treatment related difference) for both doses of TOF in comparison to PBO.

Another series of sensitivity analyses aimed to exclude the effect of data anomalies such as large changes from baseline values at the extremes of the distribution (upper 20% of values). In general, the largest changes were seen in subjects in the PBO group, but the 2 subjects with the largest mean changes from baseline in mTSS at 6 months were recorded in the TOF 5 mg group. The sponsor provided a pre-specified rank analysis and a post-hoc trimmed analysis to reduce the effect of large change values on the overall dataset. The rank analysis showed a statistically significant LS mean change from baseline to 6 months in mTSS for TOF 5 mg versus PBO ($p = 0.0237$), but not for TOF 10 mg versus PBO ($p = 0.1978$). The trimmed analysis showed a -0.37 LS mean difference at 6 months for both doses of TOF versus PBO, which were statistically significant (p value < 0.03).

The sponsor also provided a post-hoc analysis of the Campaign 1 x-ray data acquired in the second line treatment population (that is subjects who were inadequate responder to or intolerant of conventional DMARD, but not an inadequate responder to or intolerant of biologic therapy). The majority of patients in each of the three treatment groups met the definition of second line therapy: 87.5% (281/321) of subjects in the TOF 5 mg group, 89.0% (284/319) of patients in the TOF 10 mg arm and 95.0% (152/160) of subjects in the control group. Using the second line treatment population, the LS mean change from baseline to months 6 and 12 were statistically less for both TOF dose groups versus PBO.

The submission included a subset analysis of the at-risk population for structural progression. This treatment response enriched population had poor prognostic factors at baseline associated with progressive structural joint damage. Patients treated with PBO (n = 139 subjects) had greater LS mean increases from baseline in mTSS at 6 months (increase of 0.47 sharp units) and 12 months (increase of 0.92 sharp units) compared to TOF 5 mg BD (n = 277-286 subjects; increase of 0.12 and 0.29 sharp units at 6 and 12 months respectively) and TOF 10 mg BD (n = 290 to 295 subjects; increase of 0.06 and 0.05 sharp units at 6 and 12 months respectively). Each of the pairwise comparisons of each TOF dose versus PBO at 6 and 12 months for the LS mean change from baseline in mTSS in the at-risk population were statistically significant, apart from TOF 5 mg therapy versus control at 6 months for the high risk population of DAS28 [ESR] score > 5.1 at baseline ($p = 0.0975$). Pair-wise treatment comparisons also examined the LS mean change from baseline at 6 months with increasing CRP strata levels at baseline (> 3, > 7, > 10 and > 15 mg/L) and showed there were greater differences between TOF and PBO.

The mean changes from baseline in JSN scores were numerically lower, but none statistically significant for both doses of TOF at 6, 12 and 24 months versus the extrapolated PBO group.

The mean rates of progression in ES at months 6, 12 and 24 were similar for the TOF 5 mg and extrapolated PBO groups, with a modest (non-statistically significant) improvement from baseline in the TOF 10 mg group. The sponsor asserts that there was minimal change in mean ES in Campaign 2 for all three treatment groups and this may have diluted the beneficial treatment effect of TOF for the development of joint erosions.

No x-ray progression was defined as ≤ 0.5 unit increase from baseline in the relevant x-rays variable. Both TOF treatment groups had similar percentages of patients with no progression in mTSS at 12 and 24 months from baseline. However, neither dose of TOF was statistically superior to the extrapolated PBO group for this outcome.

Similar findings were observed for the incidence of subjects with no progression in ES. At 12 months, the incidence of no ES progression was 89.9% (258 out of 287) in the TOF 5 mg group, 92.95% (277 out of 298) in the TOF 10 mg arm and 87.8% (122 out of 139) in the extrapolated PBO group. At 24 months, the incidence of no ES progression was 86.7%

(249 out of 287) in the TOF 5 mg group, 89.9% (268/298) in the TOF 10 mg arm and 87.8% (122 out of 139) in the extrapolated PBO group.

Study A3921069

Study A3921069 was a Phase III, randomised, double blind, parallel group trial of 2 years duration in adult subjects with active RA who were MTX naïve (≤ 3 prior weekly doses). Enrolled subjects were randomised in a 2:2:1 ratio to one of three parallel treatment sequences: TOF 5 mg BD, TOF 10 mg BD or up-titrated oral MTX therapy (10 to 20 mg/week). The MTX control group was maintained throughout the entire 2 year period. The study included 956 patients with active RA who were either naïve to MTX or had a history of minimal exposure to MTX.

There were two primary efficacy objectives, one of which was the assessment of slowing the progression of structural damage (as measured by joint damage seen on sequential plain x-rays). The other primary efficacy objective of Study A3921069 was the ACR70 response rate at 6 months which has previously been evaluated. A secondary objective of Study A3921069 was to evaluate the durability of various levels of ACR response, clinical remission (DAS28 score < 2.6) and low disease activity (DAS28 score < 3.2) with extended treatment follow-up.

Plain x-rays were read in two distinct campaigns. Campaign 1 involved the reading of x-rays up to 12 months. For Campaign 2, all x-rays up 24 months were re-read by 2 independent, blinded readers.

A higher proportion of subjects in each TOF treatment group (71.3% in the TOF 5 mg group and 71.7% in the TOF 10 mg arm) completed 2 years of treatment compared to those in the MTX treatment group (57.0%). A total of 298 subjects (31.2%) discontinued from the trial, which included 101 patients (10.6%) withdrawing due to AEs (66 were treatment related AEs). There was a higher rate of discontinuation due to lack of efficacy in patients treated with MTX (14.0%) compared to TOF. At 2 years, the higher dose of TOF recorded the lowest rate of discontinuation due to lack of efficacy (2.8% for 10 mg BD versus 5.4% for 5 mg BD).

The three treatment groups were well balanced with respect to demographic characteristics. The majority of patients were female (79.3%; 758 out of 956) and the most frequent races recorded were White (66.1%; 632 out of 956) and Asian (17.2%; 164 out of 956). Across the three treatment groups, the mean age of patients ranged from 48.8 years in the MTX group to 50.3 years in the TOF 5 mg arm (overall age range 18 to 83 years). The majority of recruited subjects were aged between 45 and 64 years (57.8%; 553 out of 956) with a small percentage of subjects aged ≥ 65 years (10.8%; 103 out of 956).

The treatment groups were similar with respect to baseline RA disease characteristics. The mean (and median) duration of RA was 2.9 years (0.8 years) in the TOF 5 mg group, 3.4 years (0.8 years) in the TOF 10 mg arm and 2.7 years (0.7 years) in the MTX range (overall range: 0 to 44 years). All patients were to have moderate to severely active RA with joint erosions or positive RF or positive anti-CCP antibodies at enrolment. These characteristics were meant to enrich the study population for they are associated with high risk of structural damage. The majority of patients were seropositive for RA at baseline (82.4% [788 out of 956] were positive for RF and 83.7% [800 out of 956] were positive for anti-CCP antibodies). It was unclear what proportion of subjects met the inclusion criterion of radiographic erosion present at baseline.

Results for the radiographic efficacy outcomes

Statistically significant differences (that is smaller increases) in the LS mean change from baseline in the mTSS were observed for both doses of TOF versus MTX at 6, 12 and 24 months. At 24 months, both doses of TOF were observed to have ≤ 0.5 sharp unit LS mean increase from baseline in mTSS compared to just over 2 sharp units recorded in

the MTX group. At baseline, the mTSS scores ranged between 16.5 and 20.3 sharp units, so the absolute change from baseline was small in magnitude for all 3 treatment groups.

The total change in mTSS over 2 years was equally accounted for by each component score in the MTX group, and predominantly by changes over time in the JSN score for both TOF treatment groups. There was minimal change from baseline over 2 years in the ES for both TOF treatment groups, but the ES incremented upwards by almost 1 sharp unit for subjects treated with MTX. For the LS mean change from baseline over 2 years in the JSN score, there was a 0.2 to 0.4 sharp unit increase for the TOF treatment groups and > 1 sharp unit increase for the MTX arm.

Both doses of TOF showed statistically higher rates of patients with no x-ray progression compared to MTX at 6, 12 and 24 months. At 24 months, 79.9% (278 out of 348) of patients treated with TOF 5 mg BD and 83.65% (312 out of 373) of subjects treated with TOF 10 mg BD recorded a change from baseline in mTSS of ≤ 0.5 sharp units compared with 64.9% (111 out of 171) treated with MTX.

Results for the clinical efficacy outcomes

ACR70 response rates over time (up to 24 months) were statistically higher ($p \leq 0.0002$) for both doses of TOF versus MTX at all measured time points from 1 month to 24 months. At 24 months, the rate of ACR70 response was 34.4% (127 out of 369) in the TOF 5 mg group, 37.6% (148 out of 394) in the TOF 10 mg arm and 15.2% (28 out of 184) in the MTX group. In addition, the rate of sustained ACR70 response over 24 months (that is at least 6 continuous months of ACR70 response) was higher in the TOF 5 mg BD group at 28.4%(106 out of 373) and 38.5% (153 out of 397) in the TOF 10 mg BD arm compared to 14.0% (26 out of 186) in the MTX group.

Up to 24 months of follow-up, the rates of ACR20 and ACR50 response, the mean changes from baseline in HAQ-DI scores, rates of DAS28 remission (score < 2.6) and low disease activity (score ≤ 3.2) demonstrate maintenance of treatment benefit with both doses of TOF compared to MTX at all time points commencing at 1 month. The rate of ACR20 response was 69.9% (258 out of 369) at 3 months with TOF 5 mg BD therapy and remained between 64% and 72% at all time points between 3 and 24 months. For the TOF 10 mg BD group the rate of ACR20 response at 3 months was 77.9% (307 out of 394) and remained between 62% and 76% between 3 and 24 months. In contrast, the ACR20 response rate was 51.6% (95 out of 184) in the MTX arm at 3 months and remained between 42% and 55% between 3 and 24 months.

The mean changes (improvement) from baseline in HAQ-DI scores appeared to reach their maximal response at 6 months in each of the treatment groups and thereafter plateau. At 6 months, the mean improvements from baseline in the HAQ-DI score were -0.6 in the MTX group, -0.8 in the TOF 5 mg arm and -0.9 in the TOF 10 mg group.

The proportion of patients achieving DAS28 (ESR) scores of < 2.6 and ≤ 3.2 were also statistically greater in both TOF groups compared to the MTX arm, however, the response rate curves appear to be numerically higher for the higher (non-approved) TOF dose versus 5 mg BD for both endpoints at all measured time points apart from 24 months.

The x-ray results of Campaign 2 (pre-specified analysis) were consistent with the results of Campaign 1, demonstrating that both doses of TOF monotherapy (5 mg and 10 mg BD) were statistically superior compared with MTX in a first line treatment population (that is mostly MTX naïve subjects) for all primary and secondary radiographic endpoints over 2 years of treatment follow-up.

Study A3921068

Study A3921068 was an exploratory Phase II, randomised, double blind, parallel group trial in MTX naïve subjects with early active RA (≤ 2 years since diagnosis) which had the primary objective of assessing the effect of TOF 10 mg BD as monotherapy or in

combination with MTX versus MTX alone on MRI endpoints at 3 and 6 months. Subjects were randomised in a 1:1:1 design to receive either TOF 10 mg BD plus up-titrated weekly MTX, TOF 10 mg BD with weekly PBO MTX tablets, or PBO tofacitinib tablets BD with weekly MTX therapy. After a screening period of up to 28 days, randomised subjects were scheduled to attend 6 post-baseline visits (months 1, 2, 3, 6, 9 and 12).

To be eligible for inclusion, patients were required to be at least 18 years of age with a diagnosis of RA of ≤ 2 years duration, which was active at the time of enrolment (> 6 tender and swollen joints plus at least one raised serum inflammatory marker; ESR > 28 mm/hour and CRP > 7 mg/L). Patients were required to be naïve to MTX and have unequivocal evidence of at least one joint erosion on hand and wrist x-ray at screening. Subjects were also required to have evidence of clinical synovitis of an index wrist or MCP joint at screening and baseline.

The primary efficacy endpoints were: (1) the change from baseline in the OMERACT RAMRIS wrist and MCP bone marrow oedema score (range 0 to 75) at 6 months, and (2) the change from baseline in the OMERACT RAMRIS wrist and MCP synovitis score (range 0 to 24) at 3 months. Secondary efficacy endpoints included structure related outcomes such as the change from baseline in the mTSS and its components (ES and JSN score) on plain x-rays at 6 and 12 months, RAMRIS bone marrow oedema and synovitis scores at other time points, LS mean change from baseline over time in the RAMRIS erosion score, as well as clinical response measures such as ACR20/50/70 response rates and the mean change from baseline in DAS28 score.

A total of 241 subjects were screened for inclusion, and 109 patients were randomised: 36 subjects to each of the TOF treatment groups, and 37 subjects were randomised to the MTX alone arm. The majority of subjects in the TOF treatment groups (n = 27 to 28; 75 to 78% of 36) completed the study, but there was a significantly lower rate of completion in the MTX arm (56.8%; 21 out of 37). A total of 16 patients prematurely discontinued from the MTX arm, 6 due to insufficient clinical response (versus no subjects in either TOF arm), 5 because of AEs (versus 2 subjects in the TOF monotherapy group and 4 in the TOF + MTX arm), 3 withdrew consent (versus 5 in the TOF alone group and 2 in the TOF + MTX group) and 2 encountered protocol violations.

The three treatment groups were reasonably well matched for baseline features. The majority of enrolled patients were female (82.6%; 90 out of 109) and Caucasian (55.0%; 60 out of 109). The mean age was 47.8 years in the TOF + MTX and MTX groups and 50.8 years in the TOF monotherapy arm (range: 24 to 79 years). The mean duration of RA since first diagnosis was 0.8 years in the both TOF groups and 0.6 years in the MTX alone arm.

Efficacy results

Primary MRI endpoints

At 6 months, the LS mean decrease from baseline in the RAMRIS wrist and MCP bone marrow oedema score (range: 0-75) was -1.26 for the TOF+MTX group and -1.45 for TOF monotherapy arm versus 0.29 for MTX control group. The treatment related difference in the LS mean change from baseline in the RAMRIS bone marrow oedema score was -1.55 (90% CI -2.52, -0.58) for TOF+MTX and -1.74 (90% CI -2.72, -0.76) for TOF alone versus MTX, both of which were statistically significant (p = 0.0089 and p = 0.0038, respectively).

At 3 months, the LS mean decrease from baseline in the RAMRIS wrist and MCP synovitis score (range: 0 to 24) was -0.80 for the TOF+MTX group and -0.69 for TOF monotherapy arm versus -0.17 for MTX control group. The treatment related difference in the LS mean change from baseline in the RAMRIS synovitis score was -0.63 (90% CI -1.58, 0.31) for TOF+MTX and -0.52 (90% CI -1.46, 0.41) for TOF alone versus MTX, neither of which were statistically significant.

Secondary X-Ray endpoints

In the MMRM analysis at other time points (Months 1, 3 and 12), the LS mean changes from baseline in the RAMRIS bone marrow oedema scores were statistically significant in favour of both TOF treatment groups versus MTX alone at 3 and 12 months, but not at 1 month. The LS mean changes from baseline in the RAMRIS synovitis scores were statistically significant in favour of both TOF treatment groups versus MTX alone at 6 and 12 months, but not at 1 month.

The LS mean changes from baseline in the RAMRIS wrist and MCP erosion scores (range 0 to 250) were statistically significant in favour of both TOF treatment groups at 6 and 12 months, but not at 1 and 3 months. However, the absolute LS mean changes from baseline were small in magnitude and of unclear clinical significance.

The LS mean change from baseline to 6 months in the RAMRIS ES was -0.06 for TOF+MTX and -0.02 for TOF alone versus 0.65 for MTX alone. The LS mean change from baseline to 12 months in the RAMRIS ES was -0.11 for TOF+MTX and -0.08 for TOF alone versus 1.18 for MTX alone.

There was a numerically smaller change (deterioration) from baseline to 6 and 12 months with TOF treatment (alone or in combination with MTX) versus MTX alone with respect to mTSS, ES and JSN scores, however, the results are descriptive in nature only and should be interpreted with caution as the study was not powered for formal hypothesis testing and the sample size was small.

In the Spearman Rank Correlation analysis, there was a weak correlation between all of the plain x-ray outcomes and RAMRIS bone marrow oedema and synovitis scores, but a moderately strong correlation between RAMRIS erosion scores and mTSS as well as ES on Plain x-rays.

Secondary clinical endpoints

Patients who received treatment with TOF 10 mg BD (alone or in combination with MTX) had numerically higher rates of ACR response compared to those who were treated with MTX, but the differences in response were only statistically significant at earlier time points. The proportion of subjects treated with TOF+MTX and TOF alone who achieved ACR20, ACR50 and ACR70 response at 6 months using non-responder imputation (NRI) were 74.3% (26 out of 35) and 66.7% (24 out of 36), 57.1% (20 out of 35) and 47.2% (17 out of 36); and 34.3% (12 out of 35) and 30.6% (11 out of 36), respectively. In contrast, the rates of ACR20/50/70 response at 6 months using NRI in the MTX monotherapy arm were numerically lower at 46.0% (17 out of 37), 21.6% (8 out of 37) and 21.6% (8 out of 37).

Patients treated with TOF 10 mg BD (alone or in combination with MTX) showed a greater reduction DAS28 (CRP and ESR) scores over time compared with the MTX monotherapy group. At 6 months, subjects treated with TOF+MTX showed a mean -2.53 change (improvement) from baseline (5.14) in DAS28 (CRP) score which was similar to that observed in the TOF monotherapy arm (mean change of -2.75 from a baseline of 5.48). Patients treated with MTX alone had a mean -1.58 change at 6 months from baseline (5.36) in DAS28 (CRP) score.

There was no clear relationship between imaging endpoints (bone marrow oedema, synovitis and erosions) and clinical response (for example changes in DAS28 score over time) as shown in the Spearman Rank Correlation analysis.

Study A3921073

Study A3921073 was an exploratory, Phase II, randomised, double blind, parallel group, placebo-controlled trial with the primary objective of examining the effects of oral TOF 10

mg BD over 4 weeks in adults with active RA upon blood and synovial tissue biomarkers. Subjects received either TOF 10 mg BD or matching PBO tablets.

A total of 64 subjects were screened, and 15 patients were randomised to TOF 10 mg BD therapy and 14 subjects were randomised to the PBO arm. The majority of enrolled patients were female (26 out of 29) and Caucasian (23 out of 29). The mean age of all subjects was 53.3 years (range: 27 to 77 years).

Efficacy results

At 28 days, the rate of ACR20, ACR50 and ACR70 response in the TOF group was 60.0% (9 out of 15), 40.0% (6 out of 15) and 6.7% (1 out of 15), respectively, compared to no ACR responses (at any level) recorded in the control arm (n = 14 subjects).

For the TOF group, the mean number of tender joints decreased from 36.9 at baseline to 19.9 at day 28, which was a numerically greater decrease compared to the PBO arm where the tender joint count decreased from a baseline of 28.6 to 24.9 at day 28. The mean number of swollen joints decreased from baseline (22 joints) to Day 28 (13.9 joints) for the TOF group, but patients in the control arm showed an increase in the mean number of swollen joints (16.9 to 19.2 joints). The mean baseline HAQ-DI score was higher in the TOF group compared to PBO (1.76 versus 1.40) and subjects treated with TOF showed a greater improvement over 4 weeks (1.27 for TOF and 1.24 for PBO). The mean baseline CRP value was slightly higher in the TOF group (14.19 mg/L versus 10.54 mg/L in the PBO arm) and both treatment groups showed small decreases in mean CRP values.

The mean DAS28 (CRP) score decreased from a baseline value of 5.57 to 4.06 at 28 days for subjects treated with TOF compared with a smaller decrease observed in the PBO group (baseline of 5.22 to 4.91 at 28 days). A small proportion of subjects in each treatment group achieved low disease activity (DAS ≤ 3.2) at 28 days: 20.0% (3 out of 15) of subjects in the TOF arm and 14.3% (2 out of 14) of patients in the control group. No subjects reached DAS remission (score of < 2.6) at 28 days.

No apparent correlation between the PD markers (synovial tissue biopsy results and various serum cytokine levels) and DAS28 scores was observed apart from a possible relationship (correlation coefficients > 0.72) between DAS28 (CRP) score and IL-1β mRNA and IL-6 mRNA expression on synovial tissue biopsy at day 28 for subjects treated with TOF 10 mg BD.

Long term extensions studies (A3921024 and A3921041)

Pooled data from 2 long term, open label extension studies was included in this submission to support the persistence of clinical efficacy with continued tofacitinib. Study A3921024 is an ongoing LTE trial that enrolled subjects who participated and completed 1 of 15 preceding RA trials. A total of 4381 subjects have been enrolled in Study A3921024 and 1059 subjects were assigned treatment with TOF 5 mg BD and 3322 subjects were treated with TOF 10 mg BD in the LTE phase. An interim study report for this trial was provided in this submission.

Study A3921041 is a completed open label, LTE trial that was conducted in 486 Japanese patients. It enrolled subjects who participated and completed involvement in two Phase II studies (A3921039 [n = 113 subjects] and A3921040 [n = 291 subjects]) as well as Study A3921044 (n = 82 subjects). The majority of patients received TOF 5 mg BD (n = 381 subjects), but 21.6% (105 out of 486) were treated with TOF 10 mg BD. However, throughout the course of both LTE trials the dose of tofacitinib could be adjusted from 5 mg to 10 mg BD or vice versa or temporarily discontinued.

Efficacy data for both LTE studies was pooled and reported as three TOF dose groups: TOF 5 mg BD, TOF 10 mg BD and all TOF therapy (5 and 10 mg dose pooled). If the average daily dose was ≥ 15 mg then patients were assigned the TOF 10 mg BD, and if their average daily dose was < 15 mg then they were allocated to the TOF 5 mg BD group.

Up to 84 months of treatment in the pooled, open label, LTE trial dataset, both dose regimens of TOF demonstrated maintenance of clinical response as measured by the rate of ACR20 response, rate of clinical remission as determined by DAS28 (ESR) score < 2.6 and the mean improvement from baseline in HAQ-DI score. However, a limitation of the LTE trial dataset is that very few patients (50 subjects or less) were treated beyond 60 months with TOF 10 mg BD therapy. Approximately 80% of tofacitinib treated patients maintain ACR20 response up to 84 months, which is the considered the minimal most clinically relevant response. Just over 20% of tofacitinib treated subjects achieve a persistence of DAS28 clinical remission, which is a comparable figure to other DMARD therapy. The mean change from baseline in HAQ-DI score was maintained at approximately 0.5 units, which is also a similar observation to that seen with other DMARD treatment in adults with RA.

Safety

Study A3921237

Study A3921237 was a 14 week, randomised, double blind, PBO controlled, parallel group Phase II trial with the primary objective of evaluating the effect of TOF on varicella-zoster (VZV) specific immunoglobulin (Ig) responses 6 weeks after zoster vaccination in subjects with RA on concomitant MTX. The secondary objective was to evaluate the effect of TOF on VZV-specific Ig responses at 2 and 14 weeks post-vaccination. Subjects were randomised 1:1 to receive either TOF 5 mg BD or PBO. Study treatment was initiated 2-3 weeks following immunisation. A total of 112 subjects, at least 50 years of age with an active RA were included in the study (55 in the TOF 5 mg BD arm and 57 in the PBO arm). Patients were required to have a stable background dose of MTX for a minimum of 4 months prior to screening.

A total of 16 patients prematurely discontinued from the study, 4 due to drug related AEs (2 in each arm), 3 due to insufficient clinical response (2 in the PBO arm and 1 in the TOF arm), and another 9 non-drug related AEs (7 in the PBO group versus 2 in the TOF arm).

The two treatment groups were reasonably well matched for baseline features. The majority of patients were female (71.4%; 80 out of 112) and Caucasian (92.9%; 104 out of 112). The mean age of subjects in each treatment group was 62 years with the majority of subjects (52.7%; 59 out of 112) being aged between 60 and 74 years (range: 50 to 81 years). There were more patients aged ≥ 75 years in the PBO group than in the TOF group (5 versus 0).

Results for the immunogenicity safety outcomes

Overall, subjects treated with TOF 5 mg BD + MTX achieved a fold rise in VZV-specific IgG antibody levels that was similar to that seen in the PBO + MTX group. The VZV specific IgG geometric mean titre (GMT) ratios (of TOF/PBO) were slightly above 1.0 at baseline and at all subsequent visits, indicating that VZV specific IgG responses were similar between TOF and PBO throughout the trial.

At visit 2 (study day 1), the percentage of immune responders (≥ 1.5 titre rise from baseline) was higher in the TOF (55.6%; 30 out of 54) versus PBO group (47.2%; 25 out of 53) and this trend was observed at week 4 and 12 of study treatment. At day 1 and week 12, the GMFRs in VZV specific IgG levels were numerically similar between the 2 treatment groups.

Analysis of VZV specific cell mediated immunity (using ELISPOT) at 2, 6 and 14 weeks post-vaccination were numerically slightly higher in the tofacitinib group compared to PBO, but with overlapping CIs for the mean results to indicate similar vaccine induced, cell mediated immune responses between the two treatment groups.

Results for other safety outcomes

Overall, 21 subjects (36.8%) reported 39 AEs in the PBO group and 16 subjects (29.1%) recorded 40 AEs in the TOF arm. The most frequently reported types of AE were musculoskeletal disorders and infection. The most common types of infection were URTI, bronchitis, nasopharyngitis and oral herpes. All other infections were single cases, including one case each of candida infection, viral gastroenteritis, EBV infection and disseminated herpes zoster, which were only recorded in the TOF group. A total of 3 subjects in the TOF arm had a treatment related infection (5.5%).

Three subjects in the TOF group (5.5% versus. none in the PBO arm) experienced 4 SAEs including one case each of disseminated herpes zoster, bronchitis (considered drug related) and cholangitis with bile duct stone (deemed unrelated to TOF). The case of disseminated VZV infection occurred in a female subject 16 days after vaccination and two days after commencing treatment with TOF. The subject was previously varicella virus naïve. TOF was discontinued and the subject recovered without sequelae after treatment with anti-viral therapy. The subject made robust anti-varicella T-cell and antibody responses at 6 weeks post-vaccination but not at 2 weeks post-vaccination. This was interpreted as being consistent with primary VZV infection. No subjects died in this study.

In the PBO group, 15.8% (9) of subjects permanently discontinued from the study due to AEs, including 7 subjects who did so because of worsening of RA symptoms. In the TOF group, 7.3% (4) of subjects withdrew, which includes the 3 subjects who experienced SAEs as well as another patient who discontinued because of RA worsening. Another 5 subjects (1 in the PBO group and 4 in the TOF arm) had temporary treatment discontinuations or dose reductions of study treatment because of AEs, which were mainly due to intercurrent infection or laboratory abnormalities.

Among subjects with normal baseline test results, laboratory test abnormalities were recorded in 17.5% (10) of subjects in the control group and 20% (11) of patients in the TOF arm. The most frequent new laboratory test abnormalities were leucopaenia, neutropaenia, lymphopaenia, anaemia (one case each in the PBO arm), heparin induced thrombocytopenia, hypercholesteraemia and raised liver function tests (one case each in the TOF arm).

Study A3921044

Study A3921044: The final 2 year report for Study A3921044 has been previously evaluated and that information is included in the current PI. Safety information from this study contributes to the integrated safety population.

Study A3921069

Study A3921069: The interim 1 year results of Study A3921069 have previously been evaluated. The full 24 month safety dataset was considered with submission. The most common types of AEs with TOF treatment were infections, gastrointestinal disorders and abnormal investigations.

Treatment related AEs recorded only in TOF treatment groups or at a higher frequency with TOF versus MTX included increased blood CPK levels, hypertension, herpes zoster infection and hypercholesteraemia.

A total of four subjects died (3, 1 and 0 for the TOF 5 mg, TOF 10 mg and MTX groups, respectively). A case of sudden and unexplained cardiac death and a case of Non-Hodgkin's lymphoma were possibly related to study medication. One case of cardiac failure was deemed not treatment related. One death due to advanced stage colon cancer in the TOF 10mg BD group was considered not treatment related.

The proportion of subjects who experienced SAEs was comparable in each of the 3 treatment groups. Infection was the most frequent type of SAE (2.9%, 2.8% and 2.7% for

the TOF 5 mg, TOF 10 mg and MTX groups respectively). Excluding musculoskeletal disorders, gastrointestinal disorders were the second most frequent SAE (1.3%, 1.5% and 2.2%). One subject treated with TOF 5 mg therapy experienced perforation of a gastric ulcer.

The most common type of infectious SAE was pneumonia, which was recorded in two subjects in each of the TOF dose groups versus no cases in the MTX arm. One additional patient in the TOF 10 mg arm had an SAE of lower respiratory tract infection. Gastroenteritis was the second most common type of infectious SAE affecting one patient each in the TOF 5 mg and MTX groups and two subjects in the TOF 10 mg arm. Two cases of herpes zoster infection (one in each TOF dose group) were recorded, plus a patient in the TOF 10 mg arm experienced an additional case of disseminated herpes zoster infection. One subject in the MTX group developed varicella as an SAE. Other single cases of note were bone TB (TOF 10 mg) and sepsis (TOF 5 mg arm).

Regarding MACE, 2 subjects (1 in each TOF group) recorded myocardial ischaemia up to 24 months, 3 patients experienced DVT (2 subjects in the MTX arm and 1 in the TOF 5 mg group), 3 subjects developed angina (all in the TOF 5 mg group), 3 patients experienced stroke (2 in the TOF 10 mg arm and 1 in the TOF 5 mg group) and 2 patients recorded cardiac failure (1 in each TOF arm).

Of note, 1 case of demyelinating polyneuropathy was recorded in a subject treated with TOF 10 mg BD.

Neoplasms were reported at a slightly higher incidence in the TOF treatment groups (1.1% (4) in the 5 mg group and 0.8% (3) in the 10 mg group) versus MTX (0.5% (1)). Three cases of haematological malignancy were reported including Non-Hodgkin's lymphoma (TOF 5 mg group), high grade B cell lymphoma (TOF 10 mg group) and T cell chronic lymphocytic leukaemia (TOF 5 mg group).

A slightly higher percentage of subjects in the MTX arm (13.4%; 25 out of 186) discontinued due to AEs compared to both TOF dose groups (10.7% [40 out of 373] in the 5 mg group and 10.3% [41 out of 397] in the 10 mg arm). Abnormal investigation results (11 subjects) and various types of infection (8 patients) were the 2 most common reasons for treatment related AEs leading to withdrawal for patients in the TOF 5 mg group. The 11 subjects affected by abnormal investigation results included 3 cases of elevated serum transaminases, 3 cases of increased CPK levels and 2 cases of increased serum creatinine. Patients discontinuing from TOF 10 mg therapy showed a similar pattern of AEs, with the notable exception of 2 cases of TB being the precipitating treatment related AE.

In this study, 12 (3.2%) subjects in the TOF 5 mg group, 13 (3.3%) patients in the TOF 10 mg arm and 13 subjects (7%) in the MTX group met the protocol criteria for further intensive monitoring (that is elevated serum transaminases on 2 consecutive readings). Two subjects in the TOF 10 mg group and 1 subject in the MTX arm had to permanently discontinue treatment due to persistent abnormalities of liver function tests. In addition, 2 subjects (both treated with TOF 10 mg therapy) met the initial screening process of potential Hy's Law cases (that is serum ALT or AST ≥ 3 x ULN and bilirubin ≥ 2 x ULN). However both cases were subsequently dismissed.

The proportions of patients with raised serum creatinine were greater in the TOF arms than the MTX group. The proportion of patients who developed raised serum creatinine ≥ 33% of their baseline/screening value was 9.9% (37 out of 373) in the TOF 5 mg group, 9.5% (38 out of 399) in the TOF 10 mg arm and 2.7% (5 out of 186) in the MTX group. The percentage of subjects who recorded raised serum creatinine > 50% of their baseline/screening value was 1.6% (6 out of 373) in the TOF 5 mg group, 2.5% (10 out of 399) in the TOF 10 mg arm and zero in the MTX group.

The percentage of subjects who experienced a > 2 fold increase in serum CPK reading was significantly higher with TOF therapy (in a dose related manner) compared to MTX. Overall, 12.5% (46 out of 368) of subjects in the TOF 5 mg group, 22.2% (88 out of 396) of patients in the TOF 10 mg arm and 3.8% (7 out of 184) of subjects in the MTX group developed 2 fold increases in serum CPK levels. A 29 year old male in the TOF 5 mg group permanently discontinued from the trial because of rhabdomyolysis with the peak serum CPK value being 3680 U/L on study day 450. No other patients recorded rhabdomyolysis.

The median decrease from baseline in absolute neutrophil counts was -1.17, -1.57 and -0.85 x 10^9 cells/L in the TOF 5 mg, TOF 10 mg and MTX groups, respectively. There were also greater median decreases from baseline in total lymphocyte counts with TOF (5 and 10 mg therapy) compared to MTX over the 2 year period. The incidence of mild or moderate to severe neutropaenia was relatively low and comparable between the low dose TOF and MTX groups throughout the study but somewhat higher for the TOF 10 mg arm. One patient developed potentially life-threatening neutropaenia during the trial and that subject was treated with TOF 5 mg therapy. A total of 5 patients (3 in the TOF 5 mg group, and 1 each in the TOF 10 mg and MTX arms) developed thrombocytopenia. Only one subject in the TOF 5 mg group developed significant lymphopaenia which persisted on two sequential readings during the trial.

Treatment with TOF produces a significant, dose dependent increase in serum total cholesterol, which is evident by 3 months of therapy, plateaus at 6 months and remains stable thereafter up to 24 months of treatment follow-up. By 24 months, TOF 5 mg BD resulted in a mean 17.4% increase from baseline in total cholesterol and TOF 10 mg BD causes a mean 20.7% increase from baseline. Similar results with TOF were observed for low density lipoprotein levels and serum triglyceride levels.

Integrated analysis

In addition to studies A3921044 and A3921069, another 4 Phase III studies (A3921032, A3921045, A3921046 and A3921064) and 2 open label, LTE studies (A3921024 and A3921041) have contributed safety data to the integrated safety dataset. Two of the Phase III trials (A3921045 and A3921069) were TOF monotherapy studies, whereas all of the other four Phase III studies involved the addition of TOF to background DMARD, mainly MTX. All but one trial included two dose regimens of TOF (5 mg BD and 10 mg BD). The integrated safety population also included safety information from 2 Phase 1 studies (A3921030 and A3921152) and 9 Phase II studies (A3921019, A3921025, A3921035, A3921039, A3921040, A3921068, A3921073, A3921109 and A3921129).

A total of 6194 subjects with RA in the total integrated data set (P123LTE) have received at least one dose of TOF in the P123LTE population. The total patient exposure was 19405.8 PY with a mean duration of 3.13 years.

In the long term safety all exposure population (n = 4867 subjects, 14925.8 PY total exposure), the rates of overall infection with TOF 5 mg BD therapy was 43.8 events per 100 PY (95% CI 41.2, 46.55 events per 100 PY) and 47.2 events per 100 PY (95% CI 45.25, 49.16 events per 100 PY) for TOF 10 mg BD treatment. For patients on TOF monotherapy (n = 1750 subjects), the rates of overall infection were 48.9 and 41.9 events per 100 PY for 5 mg and 10 mg BD, respectively. For patients taking TOF with concomitant DMARD (n = 3117 subjects), the rates of overall infection were 41.0 and 50.3 events per 100 PY for TOF 5 mg and 10 mg BD therapy, respectively.

The incidence of serious infection was 2.38 events per 100 PY (95% CI 1.98, 2.84) for patients treated with TOF 5 mg BD and 2.97 events per 100 PY (95% CI 2.64, 3.34) for patients treated with TOF 10 mg BD. The most common types of serious infection in the long term dataset are pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis and diverticulitis, all of which are included in the proposed PI.

The incidence of adjudicated gastrointestinal perforations was low at 0 to 0.07 events per 100 PY for TOF 5 mg therapy, but significantly higher at 0.14 to 0.15 events per 100 PY in those treated with TOF 10 mg BD.

A total of 90 deaths in association with TOF therapy have been recorded in the long term safety dataset (1.45% of 6194 subjects) at an incidence rate of 0.47 deaths per 100 PY (95% CI 0.37, 0.57). Regarding the 5 mg BD regimen, 37 deaths (2.5% of 1471) have been reported at an incidence rate of 0.70 deaths per 100 PY (95% CI 0.49, 0.97), which is more than double the all-cause mortality results observed with TOF 10 mg BD (32 deaths [0.94% of 3396] at an incidence rate of 0.33 deaths per 100 PY [95% CI 0.23, 0.47]).

Other studies

The most commonly reported AEs during the first 3 months of TOF therapy in the 6 Phase III clinical trials were headache, URTI, nasopharyngitis, diarrhoea, nausea and hypertension. In the controlled portion (0-3 months) of the two Phase III monotherapy studies, the rates of overall infection with TOF 5 mg BD and 10 mg BD monotherapy were 16.1% and 17.8%, respectively, compared to 18.9% in the control group. In the controlled portion of the four Phase III studies where TOF was combined with background DMARD, the rates of overall infection in the 5 mg BD and 10 mg BD groups were 21.3% and 21.8%, respectively, compared to 18.4% in the PBO plus DMARD arm. With extended combination treatment follow-up (0 to 6 months of the three Phase III studies) where TOF plus DMARD was used, the rates of overall infection in the 5 mg BD and 10 mg BD TOF plus DMARD groups were 34.6% and 32.8%, respectively, compared to 21.3% in the PBO plus DMARD group. The most commonly reported types of infections were URTI and nasopharyngitis.

In the controlled portion of the two Phase III monotherapy studies, the rates of serious infection with TOF 5 mg BD and 10 mg BD were 0.2% and 0.3%, respectively, compared to zero in the control group. In the controlled portion of the 4 Phase III studies where TOF was combined with background DMARD, the rates of serious infection in the 5 mg BD and 10 mg BD plus DMARD groups were 0.8% and 0.8%, respectively, compared to 0.4% in the PBO plus DMARD arm. With extended combination treatment follow-up (0 to 6 months of the 3 Phase III studies), the rates of overall infection in the 5 mg BD and 10 mg BD TOF plus DMARD groups were 1.8% and 1.4%, respectively, compared to 0.5% in the PBO plus DMARD group. The most commonly reported types of serious infections were lower respiratory tract infections/pneumonia, various types of soft tissue infections and urinary tract infections.

Changes in lipid parameters from baseline through to the end of the controlled trial periods (up to 24 months) in the Phase III studies confirms that significant, dose dependent increases in serum total cholesterol, LDL cholesterol and HDL cholesterol with TOF remain stable after 3 to 6 months of drug initiation.

Risk management plan

The Pharmacovigilance and Special Access Branch has considered AUS-RMP version 2.0, 28 January 2016; data lock point 15 June 2015.

The RMP Evaluator raised no objection to the implementation of the Xeljanz RMP and requested that the pharmacovigilance plan be updated to reflect the current status of activities.

Risk-benefit analysis

Delegate's considerations

Efficacy

To support the addition of a radiological benefit claim to the current indication wording for tofacitinib, it must be demonstrated that a TOF dose of 5 mg BD has robust x-ray evidence of benefit over a 2 year treatment time frame in the population for which it is currently approved (patients with an inadequate response to or who are intolerant of MTX).

The supporting radiographic dataset was limited to Study A3921044. This study found that treatment with TOF (5 mg or 10 mg) resulted less progression from baseline in the LS mean changes in mTSS scores compared to PBO extrapolated at Months 6, 12 and 24. However, these results did not reach statistical significance for any pair-wise comparison between active treatment with TOF and PBO in the primary pre-specified analysis. Unexpectedly low rates of x-ray progression in the control group may have contributed to the findings of the primary analysis. Post-hoc sensitivity and subset analyses identified statistically less worsening of structural progression over 6 months and 12 months for TOF + MTX treatment compared to PBO + MTX. In addition to the post-hoc nature of the supportive analyses the clinical evaluator notes several limitations to the external validity of the study findings such as the a screen failure rate of 38%, insufficient dosing of MTX prior to study entry (that is < 12.5 mg/week) for unclear reasons and approximately one third of the PBO treated continued with sub-optimal MTX dosing during the study. In addition, an acceptable minimally clinically important difference in x-ray scores has not been established. The threshold of 0.5 sharp units appears to reflect the smallest detectable difference rather than a difference of clinical relevance.

Study A3921069 found that TOF therapy was associated with a lower rate of structural disease progression at 6, 12 and 24 months of treatment in a RA population with early disease who were mainly naïve to DMARD therapy. This study population is not consistent with the approved treatment indication in Australia and the sponsor is not requesting alteration to the line of therapy initiation with this submission. It is noted that approximately 40% of subjects in the MTX arm did not reach a weekly MTX dose of 17.5 to 20 mg/week for unclear reasons. This suggests a larger than expected cohort of comparator treatment subjects may have received treatment viewed as suboptimal in the Australian context. As stated above, the study population differs from the approved treatment indication (that is MTX inadequate response or intolerance).

Due to the limitations described above the x-ray benefit of TOF 5 mg BD in the Australian approved treatment population is unclear. In addition the clinical relevance of the statistically significant findings is also unclear.

Safety

The safety of tofacitinib in patients with RA has previously been assessed and no new safety concerns have been identified. However, the results of an integrated analysis have further characterised the safety profile of tofacitinib therapy.

In this submission, the sponsor has responded to the prior key issues that have impeded the registration of TOF in Australia and the EU including: the incidence and type of serious and opportunistic infection, gastrointestinal perforation, malignancy potential (particularly, lymphoma and pancreatic cancer), risk of developing interstitial lung disease, cytopenia, hepatic enzyme elevations/drug induced liver injury, elevations in serum lipids (with an atherogenic profile) and the risk of major adverse cardiovascular events.

Conclusion

In conclusion, the x-ray benefit of TOF 5 mg twice daily treatment (using data obtained in Study A3921044 and A3921069) is unclear with respect to a broad group of patients with active RA and the clinical relevance of any statistically significant observations are unclear and the sponsor's request is not supported.

Data deficiencies

There were data deficiencies with respect to clinical studies supporting the radiological benefit claim for tofacitinib 5 mg BD therapy for the approved indication. The clinical relevance of the results that demonstrated statistically significance is unclear.

Conditions of registration

The following conditions of registration are proposed, and provided here for the sponsor's comment:

- The Xeljanz Australian-specific RMP version 2.0, 28 January 2016; data lock point 15 June 2015, revised as recommended in the Round 1 evaluation, and any future updates as agreed with TGA, must be implemented as a condition of registration.
- Provide the following studies for evaluation by TGA as soon as they become available:
  - The final clinical study report for LTE Study A3921024

Questions for the sponsor

Please provide an update on the overseas regulatory status of similar submissions of the radiographic dataset.

Summary of issues

The primary issues with the submission are:

- Whether the results of the primary analysis of radiographic outcome and supporting post-hoc analyses from Study A3921044 are sufficiently robust.
- Whether the results of the primary analysis of radiographic outcome and supporting analyses from Study A3921044 are clinically relevant.
- The durability of clinical response up to 7 years.

Proposed action

The Delegate is not inclined to say, at this time, that the application for Xeljanz should be approved because the Delegate has not found the x-ray benefit of tofacitinib for the proposed treatment indication to be robust or clinically relevant.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Are the results of Study A3921044 and the supporting analyses robust enough to support the proposed indication in the approved treatment population?
2. Are the results of Study A3921044 considered clinically relevant for the approved treatment indication?
3. Is the committee satisfied that the durability of clinical response has been demonstrated for up to 7 years?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Pfizer Australia welcomes the opportunity to comment on the issues raised in the Delegate's Overview for consideration by the Advisory Committee on Medicines (ACM).

The indication sought remains as initially 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 methotrexate. Xeljanz can be used alone or in combination with nonbiological DMARDs, including methotrexate. Xeljanz has been shown to inhibit the progression of structural damage as measured by x-ray. Therapy with Xeljanz should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.*

In the response below, whilst addressing the questions raised by the Delegate, the sponsor will demonstrate that:

- Tofacitinib has shown the ability to inhibit structural damage, in patients who are methotrexate (MTX)-naïve and in those who are inadequate responders or intolerant to MTX (MTX-IR).
- The structural preservation effect can be extrapolated from a first line to a second line population as there is no argument for an artificial differentiation between patients to influence disease or patho-physiological process.
- The disease modifying properties of tofacitinib are broadly recognised by major regulators and expert committees, and must be known to prescribers to inform treatment decisions.

Therefore, the proposed updates to the tofacitinib Product Information (PI) are fully justified.

Question for the sponsor

Please provide an update on the overseas regulatory status of similar submissions of the radiographic dataset.

United States (US): The indicated population is, as for Australia, in adults with moderately to severely active RA patients who have had an inadequate response or intolerance to MTX, described as 2nd-line. The radiographic response to tofacitinib, as shown in studies A3921069 and A3921044, has been described in the US Prescribing Information (USPI) since 21 February 2014. Results from the primary endpoint, change from baseline in mTSS and the secondary endpoint of no radiographic progression, are included for both 5 mg and 10 mg twice daily (BID) doses. As in Australia, only the 5 mg BID dose is registered.

European Union (EU): The TGA is aware that ground 3 for refusal of the first MAA in July 2013 included 'uncertainties related to safety […] not offset by the benefits of treatment, […] in addition not supported by robust evidence on the prevention of structural damage at the proposed dose [5 mg BID] in the proposed treatment population.' A new MAA submitted on 4 March 2016, including the same radiographic dataset submitted to the TGA, received a positive opinion on 26 January 2017. The indication is also for 2nd-line patients and a section on radiographic response is included in the Summary of Product Characteristics (SmPC), with results from both pivotal studies at both doses.

At the time of the first MAA, the Committee for Human Medicinal Products (CHMP) shared the same concerns as the TGA regarding pivotal Study A3921044 having just missed its

primary endpoint for structural prevention at the 5 mg BID dose. However, it has since become clear that, due to a number of factors, which are explained in detail in the expert opinion, RA patients entering modern trials, particularly if they have long standing disease, show slower rates of radiological progression, making it increasingly difficult to show structural damage prevention compared to agents registered 10 years ago. As a result, the CHMP's view on how best to demonstrate inhibition of structural damage has evolved. This can be seen in revision 2 of the draft guideline for the treatment of RA, dated March 2015[7] which is an advanced version of a revision to the Points to Consider of 2003 (adopted by TGA). In particular, Section 6.3.1 states that '…as the progression of joint damage is often more prominent in the early phase of active RA disease, a study in early arthritis would be recommended to demonstrate prevention of structural damage progression.' It is therefore the rate of progression, not line of therapy, which is important to the demonstration of effect.

During the assessment of the MAA, the CHMP took this into account. Because of the robust evidence of structural preservation, maintained out to 24 months on treatment in Study A3921069, combined with the initial results and additional analyses of Study A3921044 (data provided to the TGA), the CHMP accepted that the outcome had been demonstrated. The efficacy grounds for refusal were considered to be resolved and 'the discrepancy between treatment lines [was] not of itself considered a major issue' at Day 120 of the procedure 'given that extrapolation of structural benefit from the 1st line to the 2nd and subsequent line settings is considered in principle to be valid, in the sense that a subset of patients potentially responsive to structural modifiers is likely to remain so, as one moves through the treatment line settings.'[8]

At Day 150 of the procedure, the Rapporteurs' Joint Response Assessment Report concluded: 'despite differences in the rate of radiographic progression between the 2 studies (A3921044 and A3921069), subgroups with unfavourable prognostic factors (that is, vulnerable populations with respect to progression) that did have progression while on background MTX demonstrated the benefit of adding tofacitinib 5 mg. The analysis has confirmed the structure benefit of tofacitinib in subjects that are MTX-naïve or in those that have an inadequate response to MTX. This structure benefit is evident if tofacitinib is given with and without MTX.'[9]

In summary, the EU SmPC and USPI include radiographic response data from studies A3921069 and A3921044, with 2nd-line indications, thereby endorsing tofacitinib as a structural modifier.

Other countries: Singapore is aligned with the EU and US. There have been no further developments in Canada or Switzerland since submission of the Category 1 application.

Advice requested from the ACM

1. Are the results of Study A3921044 and the supporting analyses robust enough to support the proposed indication in the approved treatment population?

The sponsor submits that the results from Study A3921044 prove structural preservation by tofacitinib 5 mg BID in the approved second line population. Indeed, in Study A3921044:

- Placebo patients demonstrated 4 times as much radiographic progression at 6 months (mean change (Δ) mTSS 0.47 units) versus. tofacitinib 5 mg BID (Δ mTSS 0.12 units).

[7] Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis (CPMP/EWP/556/95 Rev. 2) Draft, 20 March 2015.
[8] CHMP day 120 list of questions, 21 July 2016, Procedure No. EMEA/H/C/4214.
[9] Rapporteurs Day 150 Joint CHMP and PRAC Response Assessment Report, Clinical Aspects, 21 November 2016.

- The structure preserving effect of the 10 mg BID dose was even greater (Δ mTSS 0.06 units, p = 0.0376 versus. placebo), demonstrating a dose response.
- The 5 mg BID dose group showed a definite trend to benefit over placebo and, while it narrowly missed statistical significance in this study (p = 0.0792), this was an artefact of the lower than expected progression in the placebo arm, rather than a lack of effect of the medicine. Two leading experts in the field of Rheumatology have provided in-depth justification for this anomaly.[10]
- For the pre-specified and clinically meaningful endpoint[11] of 'no radiographic progression', a highly statistically significant difference was seen between 5 mg BID patients compared to placebo at Month 6 (89% versus 78%, p = 0.0055) and Month 12 (86% versus 74%, p = 0.0050). A similar effect was seen at the 10 mg BID dose.
- Sensitivity analyses showed statistically significantly less progression for 5 mg BID versus. placebo in subjects at heightened risk for radiographic progression (for example those positive for rheumatoid factor or antibodies to cyclic citrullinated peptide, with a baseline Erosion Score ≥ 3, or baseline mTSS > median), a population representing 80% of patients seen in a leading rheumatology centre in Queensland.

The sponsor believes that to only consider the above data for the assessment of tofacitinib's structural modification properties, on the basis of an artificial distinction between patients who have not been treated with MTX and those that have, is not justified. This is explained below.

Relevance of structural preservation seen in Study A3921069

That Study A3921069 had a clearly positive outcome in demonstrating evidence of superior structural preservation with tofacitinib 5 mg BID compared with MTX at 6, 12 and 24 months, has not been contested. Indeed, this was demonstrated by highly statistically significant differences in Δ mTSS, with 66% less mean progression in mTSS at 6 months for 5 mg BID versus MTX (p = 0.0006), maintained over 2 years, and rates of no progression at 6 months of 12.9% for tofacitinib 5 mg BID versus 26.4% for MTX (p = 0.0004), also maintained over 2 years.

However, there remains a difference in interpretation between the sponsor and the TGA, regarding the relevance of Study A3921069 data to the approved patient population. The sponsor maintains that, even though the study was conducted in MTX-naïve, first line patients, extrapolation of structural benefit from first line to second and subsequent line settings is considered valid for the following reasons:

- There are no data suggesting that MTX-IR and MTX-naïve patients have different patterns of disease.
- 'Line of therapy' and 'early' versus 'late' RA are artificial constructs and do not represent different pathologic processes of disease. Indeed, early RA now refers to the first 12 to 24 months after diagnosis rather than 5 years of disease as historically defined.[12] Thus, a stoic patient with longstanding, but moderate untreated RA who finally agrees to MTX is considered first line, while a rapidly progressing severe early RA patient who is intolerant to MTX and fails a TNF inhibitor (TNFi) is considered third line.
- The features of the synovium are similar in early RA and longstanding disease, indicating that no patho-physiological arguments currently exist for the effect of

[10] Landewé RB, et al. Is radiographic progression in modern rheumatoid arthritis trials still a robust outcome? Experience from tofacitinib clinical trials. *Arthritis Research & Therapy* 18:212 (2016).
[11] Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis (CPMP/EWP/556/95 Rev. 2) Draft, 20 March 2015.
[12] Scott DL. Early rheumatoid arthritis. *Br Med Bull.* 81-82: 97-114 (2007).

therapeutic intervention on synovial inflammation varying between different stages of the disease.

- The currently available DMARDs, bDMARDs, and tsDMARDs for the treatment of RA have altered the expected course of the disease. 'Current therapy for RA is such that progression from symptom onset to significant disability is now no longer inevitable.'[13]
- Regulatory guidance is evolving as well; in recognition of this, and as previously noted, recommends a study in early arthritis to demonstrate prevention of structural damage progression.[14] The ability to preserve structure is regarded as an inherent effect of the compound irrespective of the line of therapy.
- Approved biological DMARDs, and TNF inhibitors in particular, have shown structural preservation in both lines of therapy and early and late stages of disease. 'Remarkable consistency in the extent of the interference with progression of structural damage by all TNF inhibitors in patients with early or late RA' was noted in a comparative analysis of trials with infliximab, adalimumab, rituximab, abatacept, certolizumab, and tocilizumab.[15] The authors also noted that 'the range of the structural effects exerted by TNF blockade plus methotrexate treatment are strikingly similar in patients with early and late RA, which is in contrast to the differences in clinical and functional efficacy (much more pronounced in early than late RA). Thus, we infer that the final pathways to joint destruction in patients with RA do not become refractory to cytokine-blocking treatment with increasing disease duration, or with an increasing number of previous failed therapies.'[16]
- Whilst tofacitinib was first in its class of JAK inhibitors, data have now become available that demonstrate an effect of JAK inhibitor baricitinib (recently approved in Europe) on structural progression in moderately to severely active RA patients, both MTX-naïve and MTX-IR.[17] Tofacitinib and baricitinib have been grouped in a new target synthetic DMARD (tsDMARD) category in the latest EULAR guidelines.[18]

Therefore, the sponsor proposes that, perhaps in much the same way:

- The non-significant results for structural preservation from golimumab Study C0524T06 in MTX-IR patients[19] represent an exception amongst the totality of evidence for golimumab in particular and TNF inhibitors in general, due to methodological artefacts,
- The non-significant result for structural preservation from tofacitinib Study A3921044 in MTXIR patients represents an exception amongst the totality of evidence for tofacitinib in particular and JAK inhibitors in general, due to a similar methodological artefact.

Convergence across endpoints and persistence of efficacy

[13] Upchurch K, Kay J. Evolution of treatment for rheumatoid arthritis. *Rheumatology* 51: vi28- vi36 (2012).
[14] Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis (CPMP/EWP/556/95 Rev. 2) Draft, 20 March 2015.
[15] Smolen JS, et al. The pathogenesis of rheumatoid arthritis: new insights from old clinical data? *Nat. Rev. Rheumatol.* 8: 235-243 (2012).
[16] Smolen JS, et al. The pathogenesis of rheumatoid arthritis: new insights from old clinical data? *Nat. Rev. Rheumatol.* 8: 235-243 (2012).
[17] Olumiant (baricitinib), Committee for Medicinal Products for Human Use, Assessment Report, 15 December 2016.
[18] Smolen JS, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis.* 76: 960-977 (2017).
[19] AusPAR Simponi and Simponi Smartject injector; golimumab (rmc); Janssen-Cilag Pty Ltd. PM-2012- 01202-3-3, Date of Finalisation 16 August 2013.

The significant effects on the Health Assessment Questionnaire Disability Index (HAQ-DI) and disease activity score 28 joints (DAS28-4) erythrocyte sedimentation rate (ESR) add supporting value to the radiographic findings, as correlations between these endpoints have been established.

In Study A3921044, 7.17% of patients receiving tofacitinib 5 mg BID achieved DAS28-4(ESR) < 2.6 at 6 months, a measure of remission, compared with only 1.5% of patients in the placebo arm (despite treatment advancement to tofacitinib in some patients at 3 months and continuation of background MTX in all). HAQ-DI scores (for which the minimal clinically important difference is 0.22)[20] for tofacitinib treated patients decreased at 3 months, by 0.40 versus 0.15 for placebo, indicating improved physical function in these patients. Pooled analyses of long term extension studies demonstrated persistence of efficacy for these endpoints with tofacitinib treatment for up to 7 years.

MTX dose in Study A3921044 reflects real world

TGA has considered the dose of MTX received by patients prior to and during Study A3921044 to have been 'sub-optimal' and a ground for questioning the validity and applicability of the data to the Australian setting.

In Study A3921044, however, the median weekly dose of preceding methotrexate use was 15 mg for all treatment groups. The mean area under the plasma concentration-time curve (AUC) of MTX starts plateauing at 15 mg per week and there is no further increase in AUC when the oral dose administered is 25 mg relative to 20 mg. In addition, 'the 'optimal' dose of MTX needed to preserve structural benefit is unknown' and the dose administered is patient specific. Studies supporting treatment with MTX in RA used doses of 10 to 25 mg, as either monotherapy or in combination with other drugs.[21]

In Australia, an analysis of 'MTX dosing in 1200 consecutive RA patients with established disease [revealed that,] for a variety of reasons, 36% of patients regularly take 10 mgs or less MTX per week and another 15% dose between 10 and < 20mgs per week. The mean dosing of 15 mgs MTX per week in these trials is consistent with real life clinical practice.'[22]

Therefore, the dose of MTX before and during the study was consistent with common practice in Australia and, as previously noted, with other published studies of registered DMARDs.

Overall conclusion

The preponderance of evidence demonstrates that inhibition of structural damage with tofacitinib is based on sound, scientifically valid and robust data, is supported by other major regulators and clinical experts, and should therefore be described in the Australian PI.

2. Are the results of Study A3921044 considered clinically relevant for the approved treatment indication?

In regards to radiographic response, using mTSS as the endpoint serves to prove, within a relatively short timeframe in clinical trials, whether or not a medicine is able to modify the pathophysiological processes leading to joint destruction. This is what differentiates disease-modifying agents from anti-inflammatory drugs.

[20] Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: A review of its history, issues, progress, and documentation. *J Rheumatol.* 30: 167-78 (2003); Kosinski M, et al. Determining minimally important changes in generic and disease-specific health-related quality of life questionnaires in clinical trials of rheumatoid arthritis. *Arthritis Rheum.* 43: 1478-87 (2000).
[21] Weinblatt ME. Methotrexate in Rheumatoid Arthritis: A Quarter Century of Development. *Trans Am Clin Climatol Assoc.* 124: 16-25 (2013).
[22] Nash P, Nicholls D. Perceptions of methotrexate use in rheumatoid arthritis by rheumatologists and their patients: an Australian survey study. *Int. J. Rheum. Dis.* 16: 652-661 (2013).

For reasons mentioned earlier, the magnitude of change seen in more recent trials, and especially in patients with long established disease, may be less than before the advent of DMARDs. However, the mTSS scale is sufficiently sensitive to detect a difference of ≥ 0.5 units and to establish whether structural damage is progressing or not, which is the relevant outcome.

If the progression seen over 2 years in the comparator arms of the A3921044 and A3921069 studies, whilst appearing to be relatively small, continued over the longer term, the consequences to patients could include irreversible joint damage and progressive disability.

The Delegate has noted the clinical evaluator's concern regarding 'the magnitude and clinical relevance of the potential x-ray benefits with [tofacitinib] versus alternative treatment options'. Whilst direct comparison of radiographic outcomes between tofacitinib and approved biological DMARDs is not available, the sponsor has previously shown that changes in mTSS from baseline for tofacitinib were overall comparable with those of certolizumab, tocilizumab and golimumab. The magnitude of effect seen in patients with moderately to severe active RA for JAK inhibitor baricitinib, which was recently approved in Europe, is also comparable.[23]

The Delegate and clinical evaluator agree that 'an impact on inhibiting the structural bone damage of RA is associated with better long term patient outcomes particularly regarding maintenance of physical function and quality of life.' There is therefore no doubt that the ability to inhibit progression of this damage, which tofacitinib has been proven to have, is most clinically relevant.

3. Is the committee satisfied that the durability of clinical response has been demonstrated for up to 7 years?

It is important for prescribers to make informed decisions about long term treatment of RA patients given the chronic and frequently progressive nature of their disease.

The persistence of tofacitinib's effect was clearly demonstrated for 2 years in controlled Phase III studies A3921044 and A3921069. Durability of effect was assessed by ACR20, ACR50, ACR70 response rates, mean change (Δ) in HAQ-DI, and mean DAS28-4(ESR) measuring disease activity.

In open label LTE studies A3921024 and A3921041, tofacitinib 5 and 10 mg BID demonstrated sustained efficacy through 84 months of treatment as measured by ACR20, DAS28-4(ESR) < 2.6 response rates and improvement in physical function (Δ HAQ-DI).

Persistent achievement of low disease activity, a major treatment target, has been shown to stabilise functional ability and reduce radiologic progression of disease[24] making the durability of response to tofacitinib compelling and adding further plausibility to the preserving effects seen on structural progression.

Benefit/risk

Tofacitinib 5 mg BID 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

[23] Olumiant (baricitinib), Committee for Medicinal Products for Human Use, Assessment Report, 15 December 2016; Dougados M, et al. Baricitinib in patients with inadequate response or intolerance to conventional synthetic DMARDs: results from the RA-BUILD study. *Ann Rheum Dis.* 76: 88-95 (2017); Taylor PC, et al. Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. *N Engl J Med.* 376: 652-662 (2017).
[24] van den Broek M, et al. BeSt practice: The success of early-targeted treatment in rheumatoid arthritis. *Clin Exp Rheumatol.* 30(Suppl 69): S35-S38 (2012); Allaart C, et al. Treatment of recent-onset rheumatoid arthritis: Lessons from the BeSt study. *J Rheumatol Suppl.* 2007; 80: 25-33 (2007).

(CRP and ESR) and, therefore, the underlying inflammatory process. The totality of evidence supports a structure preserving effect in both MTX-naïve and MTX-IR RA patients, consistent with the structural benefits of bDMARDs and JAK inhibitor baricitinib.

The Delegate has acknowledged that, from the safety perspective, 'in this submission, the sponsor has responded to the prior key issues that have impeded the registration of [tofacitinib] in Australia and the EU'. There were no new safety concerns identified in this submission and, therefore, the benefit/risk of tofacitinib in the indicated population remains positive.

Advisory Committee Considerations[25]

The ACM taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and did not support the proposed extension of indications for Xeljanz immediate release tablet containing 5 mg (tofacitinib as citrate) for the additional indication below:

> *XELJANZ has been shown to inhibit the progression of structural damage as measured by x-ray.*

In making this recommendation the ACM noted:

- The findings of the primary x-ray analysis of Study A3921044 were not supportive of an x-ray claim for TOF therapy in a predominantly second line treatment population with established RA.
- Low rates of x-ray progression in the control group in Study A3921044 may explain the lack of finding of structural benefit in the primary analysis but this explanation is not an acceptable justification for not confirming structural benefit.
- The magnitude and clinical relevance of the x-ray benefits of TOF with active RA were not sufficient to support the proposed indication.
- Concerns with low MTX dosing prior to enrolment in one third of patients.
- Post-hoc and sensitivity analyses to demonstrate structural benefit are not considered as robust as the primary analysis for demonstrating structural benefit.
- The inclusion of radiographic response data from study A3921044 in the clinical trials section of the PI was supported but the data from study A3921069 was considered less relevant as the patient population was inconsistent with the line of therapy for which TOF is currently approved in Australia.
- The committee noted that historically, endpoint claims have been included in the indication for some drugs for the treatment of rheumatoid arthritis, but that in the future this information would better placed in the clinical trials section in the PI.

Specific advice

ACM advised the following in response to the Delegate's specific questions on the submission.

[25] ACM provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia, including issues relating to pre- and post-market functions for medicines. ACM is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. ACM was established in January 2017 replacing the Advisory Committee on Prescription Medicines (ACPM), which was formed in January 2010. ACM encompasses pre- and post-market advice for medicines following the consolidation of the previous functions of the ACPM, the Advisory Committee on the Safety of Medicines (ACSOM), and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

1. *Are the results of Study A3921044 and the supporting analyses robust enough to support the proposed indication in the approved treatment population?*

ACM advised that the modified Total Sharp Score (mTSS) results presented in Study A3921044 do not support a robust case for the proposed indication relating to structural benefit deriving from TOF 5 mg BD In the primary analysis the point estimates of the placebo and 5 mg BD arms were not statistically significantly different, possibly as a result of the lower than expected progression of the placebo group. The post-hoc and sensitivity analyses were generally supportive of an effect on structural damage but were not considered robust enough to support the proposed indication.

2. *Are the results of Study A3921044 considered clinically relevant for the approved treatment indication?*

ACM advised that the recorded mean changes in mTSS were small and probably not clinically significant. Subgroups of patients with risk factors for structural damage may benefit more from tofacitinib treatment. Supporting studies suggest that tofacitinib has a positive effective on structural damage but possibly not at a clinically significant level.

3. *Is the committee satisfied that the durability of clinical response has been demonstrated for up to 7 years?*

ACM advised that clinical response has been reasonably demonstrated to 5 years with small numbers of patients maintaining a response at 7 years. ACM concluded that the submitted evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of Xeljanz immediate release tablet containing 5 mg of tofacitinib (as citrate) for the proposed indication.

Post ACM negotiations

The Delegate in correspondence with the sponsor (dated 21 April 2017) recommended the following:

The Delegate considered and accepted the committee's advice and reviewed the sponsor's Pre-ACPM response. The Delegate proposed to reject the addition of a radiographic benefit claim to the indications for Xeljanz, however, other proposed changes may become acceptable if issues in relation to the Product Information are satisfactorily addressed.

The sponsor's response (dated 8 May 2017) proposed the following revision to the wording of the indications:

- Remove the statement regarding the inhibition of structural damage.
- The deletion of 'signs and symptoms of' is considered acceptable.

The revised indication as accepted by the sponsor 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 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.*

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Xeljanz (tofacitinib [as citrate]) immediate release tablet 5 mg for the new 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 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.

Specific conditions of registration applying to these goods

- The tofacitinib Australian-specific RMP, version 2.0, 28 January 2016; data lock point 15 June 2015, revised as recommended in the Round 1 evaluation and as per the sponsor's email included with submission, and any subsequent revisions, as agreed with TGA will be implemented in Australia.
- The following study reports must be submitted to the TGA as soon as possible after completion, for evaluation as Category 1 submission: The final clinical study report for LTE Study A3921024.

Attachment 1. Product Information

The PI approved for Xeljanz at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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