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

September 2019

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
5-ASA	5-aminosalicylic acid
6-MP	6-mercaptopurine
AE	Adverse event
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AZA	Azathioprine
BCC	Basal cell carcinoma
BID	Bis in die (twice a day)
BP	Blood Pressure
CHMP	Committee of Medicinal Products for Human use
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CMI	Consumer Medicines Information
CMV	Cytomegalovirus
CP-690,550	Tofacitinib (drug development code)
CPK	Creatine phosphokinase
CRF	Case report form
CRP	C-reactive protein

Abbreviation	Meaning
CV-EAC	Cardiovascular Endpoint Adjudication Committee
CYP3A	Cytochrome P450, family 3, subfamily A
DILI	Drug-induced liver injury
DMARD	Disease-modifying anti-rheumatic drug
DRESS	Drug reaction with eosinophilia and systemic symptoms
EBV	Epstein-Barr virus
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GIPRC	Gastrointestinal Perforation Review Committee
GLMM	Generalised linear mixed model
HDL	High-density lipoprotein
HERC	Hepatic Event Review Committee
hsCRP	High sensitivity C-reactive protein
HZ	Herpes zoster
IBD	Inflammatory bowel disease
ICH	International Conference on Harmonisation
IL	Interleukin
ILD	Interstitial lung disease
ILDRC	Interstitial Lung Disease Review Committee
IndNR	Induction non-responder
IR	Incidence rate

Abbreviation	Meaning
IV	Intravenous
IVRS	Interactive voice recording system
JAK	Janus kinase
JIA	Juvenile idiopathic arthritis
LDL	Low-density lipoprotein
LFT	Liver function test
LLN	Lower limit of normal
LOCF	Last observation carried forward
MAC	Malignancy Adjudication Committee
MACE	Major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
mL	Millilitre
mm Hg	Millimetres of mercury
MMRM	Mixed-effects model repeated measures
ms	Millisecond
MTX	Methotrexate
N (or n)	Number
NMSC	Non-melanoma skin cancer
NNT	Numbers needed to treat
NRI	Non-responder imputation
OI	Opportunistic infection
OIRC	Opportunistic Infection Review Committee
OL	Open label
OPC	Oral powder for constitution
PD	Pharmacodynamic(s)
PI	Product Information

Abbreviation	Meaning
PK	Pharmacokinetic(s)
PMAR	Population modelling analysis report
PopPK	Population pharmacokinetic analysis
PPAS	Per Protocol Analysis Set
PsA	Psoriatic arthritis
PsO	Psoriasis
PSUR	Periodic Safety Update Report
PT	Preferred Term
PY	Patient-year
QoL	Quality of life
RA	Rheumatoid arthritis
RMP	Risk management plan
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Standard deviation
SE	Standard error
SmPC	Summary of Product Characteristics
SOC	System Organ Class
STAT	Signal transducer and activator of transcription
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TGA	Therapeutic Goods Administration
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
UC	Ulcerative colitis
ULN	Upper limit of normal

Abbreviation	Meaning
URTI	Upper respiratory tract infection
US(A)	United States (of America)
USPI	United States Package Insert
WBC	White blood cell

I. Introduction to product submission

Submission details

Type of submission:	Extension of indication and major variation (new strength)
Decision:	Approved
Date of decision:	11 February 2019
Date of entry onto ARTG:	19 February 2019
ARTG numbers:	196987, 233439, 298307
, *Black Triangle Scheme*	Yes This product will remain in the scheme for 5 years, starting on the date the new indication was approved.
Active ingredient:	Tofacitinib (as citrate)
Product name:	Xeljanz
Sponsor's name and address:	Pfizer Australia Pty Ltd Level 17, 151 Clarence Street Sydney, NSW, 2000
Dose form:	Film coated tablet
Strengths:	5 mg and 10 mg
Containers:	Bottle (5 mg tablets), blister pack (5 and 10 mg tablets)
Pack sizes:	Bottle: 60 and 180 tablets, blister pack: 14 (sample size) and 56 tablets
Approved therapeutic use:	*Ulcerative colitis* *Xeljanz is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.*
Route of administration:	Oral
Dosage:	For ulcerative colitis: 10 mg twice daily for induction for 8 weeks and 5 mg twice daily for maintenance. For further details refer to the Product Information (PI).

Product background

This AusPAR describes the application by Pfizer Australia Pty Ltd (the sponsor) to register a new 10 mg tablet strength of Xeljanz (tofacitinib as citrate) and to extend the indications of the previously approved 5 mg tablet to include the following indication:

> *Ulcerative colitis*
>
> *Xeljanz is indicated for the induction and maintenance of treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to conventional therapy.*

Ulcerative colitis (UC) is a chronic, relapsing, inflammatory disease of the colon characterised by alternating episodes of spontaneous remission and relapse. The pathogenesis of UC involves the complex interaction of genetic predisposition, epithelial barrier defects, dysregulated host immune responses and environmental factors. Clinically, UC is characterised by colonic mucosal ulceration.

Current treatment options for moderately to severely active UC include: corticosteroids; immunosuppressants such as azathioprine (AZA) and 6-mercaptopurine (6-MP); tumour necrosis factor inhibitors (TNFi) such as infliximab, adalimumab and golimumab; and the anti-integrin treatment, vedolizumab. Corticosteroids are used during acute flare, however they are associated with significant problems with intolerance and side effects, and have no role in maintenance. A substantial proportion of patients with moderately to severely active UC fail to respond to TNFi agents either initially or lose their initial response. There is a significant unmet need in patients with moderately to severely active UC who have previously failed corticosteroids, AZA/6-MP, or biologics such as TNFi. Importantly, there is no single current therapeutic option that offers fast onset of action, strong induction and maintenance efficacy, as well as efficacy in the most difficult to treat patient population. The gastroenterology field is in need of a treatment that offers an advance from 5-ASA, is not a steroid or biological disease modifying anti-rheumatic drug (DMARD), and is not an injection.

Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of haematopoiesis and immune cell function. Inhibition of JAK1 and JAK3 by tofacitinib blocks signalling through the common gamma chain-containing receptors for several cytokines, including interleukins (IL)-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, proliferation and function, and inhibition of their signalling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signalling by additional pro-inflammatory cytokines, such as IL-6 and type I and II interferons.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG, Submission PM-2012-00788-3-3) as a 5 mg tablet blister pack (ARTG 196987) and bottle (ARTG 233439) on 5 February 2015 for the following indication:

> *Xeljanz is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. Xeljanz con be used alone or in combination with non-biological disease-modifying anti-rheumatic drugs (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.*

On 1 June 2017 (Submission PM-2016-00757-1-3) the following changed indications were approved:

> *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.*

On 8 November 2018 (Submission PM-2017-03802-1-3) the following extension of indications was approved:

> *Psoriatic Arthritis*
>
> *Xeljanz in combination with conventional synthetic DMARDs is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response to a prior DMARD therapy*

Following this, the full approved indications at this time were:

> *Rheumatoid arthritis*
>
> *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 con be used alone or in combination with non-biological disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate.*
>
> *Psoriatic Arthritis*
>
> *Xeljanz in combination with conventional synthetic DMARDs is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response to a prior DMARD therapy*

At the time the TGA considered this application, a similar application had been approved in EU (centralised procedure) 26 July 2018, USA 30 May 2018, Canada 11 September 2018 and was under consideration in Switzerland (Table 1).

Table 1: Foreign regulatory status of similar applications as of 20 November 2018

Region	Submitted	Status	Indication
EU (centralised procedure)	[Information redacted]	Approved (26 July 2018)	*Tofacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent (see section 5.1)*
USA	[Information redacted]	Approved (30 May 2018)	*Xeljanz is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).* *Limitations of Use: Use of Xeljanz in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.*

Region	Submitted	Status	Indication
Canada	[Information redacted]	Approved (11 September 2018)	*Xeljanz (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) with an inadequate response, loss of response or intolerance to either conventional UC therapy or a TNFα inhibitor.* *Limitations of Use: Use of Xeljanz in combination with biological UC therapies or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.*
Switzerland	[Information redacted]	Under review	Under review.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR 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 time line

Table 2 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2017-04764-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	31 January 2018
First round evaluation completed	29 June 2018
Sponsor provides responses on questions raised in first round evaluation	30 August 2018
Second round evaluation completed	18 October 2018
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	1 November 2018
Sponsor's pre-Advisory Committee response	20 November 2018
Advisory Committee meeting	6 December 2018
Registration decision (Outcome)	11 February 2019

Description	Date
Completion of administrative activities and registration on ARTG	19 February 2019
Number of working days from submission dossier acceptance to registration decision*	195

*Statutory timeframe for standard applications is 255 working days

Evaluations included under Quality findings and Nonclinical findings incorporate both the first and second round evaluations.

III. Quality findings

Introduction

The sponsor has submitted an application to register a new strength of the already registered Xeljanz (tofacitinib as citrate) 5 mg film coated tablet, blister pack (ARTG 196987) and bottle (ARTG 233439). This is part of an application for an extension of indications.

There are no pharmacopoeial monographs for the active ingredient or finished product.

Drug substance (active ingredient)

No change in drug substance manufacture by the product manufacturer has been introduced since the initial assessment.

Drug product

The sponsor states that the 10 mg and 5 mg tablets are manufactured from a common blend using the same manufacturing process. The two strengths are quantitatively proportional and are differentiated by colour and debossing.

The proposed drug product (10 mg tablets) are blue, film coated, round tablets debossed with 'Pfizer' on one side and 'JKI 10' on the other. The proposed drug product will be packaged in high density polyethylene bottles with desiccant and induction seal, or in aluminium foil/foil blisters. The blue 10 mg tablets are colour differentiated from white 5 mg tablets.

Quality summary and conclusions

Approval for registration of the proposed 10 mg product is recommended from a pharmaceutical chemistry perspective. The following details relate to the application.

- No change in drug substance manufacture or control by the product manufacturer has been introduced since the initial assessment.
- A shelf life of 36 months with the storage condition, 'store below 30°C' is recommended.
- The labels of the drug products are acceptable from a TGA perspective.

- The finished product specification for Xeljanz tofacitinib (as citrate) 10 mg film coated tablet is acceptable from a TGA perspective.
- The proposed trade name Xeljanz is already registered.
- The provisional ARTG records have been amended by the evaluator after verification by the sponsor.
- The PI for combined 5 and 10 mg tablets is acceptable from a TGA point of view.
- The GMP clearances for all overseas manufacturing sites below are valid.
- The sponsor has requested to withdraw their 10 mg bottle presentation. Their request has been accepted.

Xeljanz 10 mg tablet was previously assessed by the TGA in 2012 (submission PM-2012-00788-3-3) and was deemed acceptable from a TGA point of view. The sponsor withdrew the application prior to the registration. The current application is a resubmission of the previously provided data for the 10 mg tablet. Approval for registration of the proposed product is recommended from a pharmaceutical chemistry perspective.

Bioequivalence between Phase IIb, Phase III and the commercial tablets was evaluated in Study A3921075. Absolute bioavailability of active ingredient was investigated in Study A3921077 using the commercial tablet and an intravenous (IV) formulation. Bioavailability of Phase IIa tablets relative to oral powder for constitution (OPC) was examined in Study A3921005. In addition, the effect of food on the bioavailability of active ingredient was evaluated in Studies A3921005 (Phase IIa tablet) and A3921076 (commercial tablet). These studies have been evaluated in detail during the initial application.

IV. Nonclinical findings

Introduction

The sponsor has submitted an application to vary the conditions of registration of Xeljanz, oral formulation of tofacitinib (as citrate), 5 mg film coated tablet (ARTG: 196987, 233439):

- To extend the indications for Xeljanz (tofacitinib) tablets to include the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to conventional therapy.
- To increase the strength and maximum daily dose Xeljanz tofacitinib (as citrate) from 5 mg to 10 mg film coated tablet. The recommended dose for adult patients is 10 mg twice daily (BID) for induction for at least 8 weeks and 5 mg BID for maintenance. The 10 mg tablets are manufactured from a common blend of the approved 5 mg tablets using the same manufacturing process. The two strengths are quantitatively proportional and are differentiated by colour and debossing.

At the time of this application Xeljanz (tofacitinib citrate) 5 mg tablets were currently approved for the treatment of moderate to severe active rheumatoid arthritis (RA) in adults who have had an inadequate response or are intolerant to methotrexate (MTX)(submission PM-2012-00788-3-3).

In support of the proposed changes, the sponsor submitted i*n vitro* and *in vivo* pharmacology and pharmacokinetic studies as well as *in silico* impurity studies (in the nonclinical dossier). All of the nonclinical data submitted in this application has been

previously evaluated in submission PM-2017-03802-1-3 in support of the psoriatic arthritis (PsA) extension of indication.

No new nonclinical data or nonclinical pharmacology models of immune bowel disease (including ulcerative colitis) were conducted to evaluate tofacitinib since the overall clinical predictability of these models is low.

Rationale and mechanism of action

UC is a chronic inflammatory disorder of the colon, whose pathogenesis involves the complex interaction of genetic predisposition, epithelial barrier defects, dysregulated host immune responses, and environmental factors.

Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome.

The JAK family, including JAK1, JAK2, JAK3, and tyrosine kinase 2 (TyK2), is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with cytokine receptors for several cytokines, including interleukin IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21.

Upon binding of the cytokine to its receptor, the associated JAKs are activated, and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the signal transducer and activator of transcription (STAT) family (1, 2, 3, 4, 5a, 5b, and 6) of transcription factors. The STATs are then phosphorylated and translocated to the nucleus where they bind to specific gene promoters to activate transcription of a range of target genes.

In addition, inhibition of JAK1 will result in attenuation of signalling by additional pro-inflammatory cytokines, such as IL-6, IL- 22 and interferon (IFN) gamma (IFN γ).

These cytokines are integral to lymphocyte activation, development, homeostasis, proliferation, and function; therefore, inhibition of their signalling may result in modulation of multiple aspects of the immune response.

Animal models as well as genome-wide association studies have demonstrated the importance of the JAK/STAT pathway in the pathogenesis of immune-mediated inflammatory conditions.

Genetic polymorphisms in the JAK/STAT pathway have been associated with ulcerative colitis in humans, thus emphasizing the importance of this pathway in disease pathogenesis.

The modulatory effects of JAK inhibition on multiple cytokine pathways central to the pathogenesis of ulcerative colitis provide the scientific rationale for using tofacitinib for the ulcerative colitis indication.

Toxicology

Relative exposure

Population PK analysis results;[1] indicated that tofacitinib plasma exposure, as measured by the steady state area under the concentration time curve (AUC) after 5 or 10 mg BID is similar(differences in geometric means within 20%) between UC and other patient populations such as RA and psoriasis (PsO) Exposure margins for the 10 mg BID dose regimen were previously calculated in application PM-2012-00788-3-3 and high multiples

[1] Clinical Population PK Report PMAR-EQDD-A392i-sNDA-513; 19 Dec 2016

of the anticipated clinical systemic exposures were attained in the pivotal toxicology studies.

Nonclinical summary and conclusions

The pharmacology of tofacitinib, based on the literature presented, supports the new indication.

Demonstration of tofacitinib efficacy in ulcerative colitis will rely on the clinical data though it is noted that previous nonclinical data showed anti-inflammatory efficacy in animal models of RA and PsA.

Relative exposure margins in the previously evaluated toxicology studies were high for the 10 mg BID clinical dosing regimen and raise no extra safety concerns.

There are no objections on nonclinical grounds to the proposed changes to the registration of Xeljanz.

V. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Information on the condition being treated

Ulcerative colitis is a chronic, relapsing, inflammatory disease of the colon characterised by alternating episodes of spontaneous remission and relapse. The pathogenesis of UC involves the complex interaction of genetic predisposition, epithelial barrier defects, dysregulated host immune responses and environmental factors. Clinically, UC is characterised by colonic mucosal ulceration. Its course is characterised by intermittent flares interposed between variable periods of remission. The disease may present at any age, with peak incidence from the second to the fourth decades. Incidence of UC has increased consistently worldwide over the past 50 years.

The primary goal of therapy for UC is to rapidly induce remission when the disease is in an acute flare and to maintain remission without long-term use of corticosteroids, while improving and maintaining a satisfactory quality of life (QoL). Further goals include the minimisation of disease and treatment complications, and avoidance of surgery. As noted in the European Medicines Agency (EMA) guideline on ulcerative colitis,[2] 5-aminosalicylic acid (5-ASA) may be considered the mainstay of therapy for mild to moderate UC, but is not specifically indicated for treatment of moderately to severely active disease.

Current treatment options

Current treatment options for moderately to severely active UC include corticosteroids, immunosuppressants such as AZA and 6-MP, TNFi such as infliximab, adalimumab and golimumab, and anti-integrin treatments such as vedolizumab.

Corticosteroids are used during acute flare. However, corticosteroids are associated with significant problems with intolerance and side effects, and have no role in maintenance. A

[2] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), 24 January 2008, Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis, CHMP/EWP/18463/2006.

substantial proportion of patients with moderately to severely active UC fail to respond to TNFi agents either initially (primary non-response) or lose their initial response (secondary non-response). Patients who have failed TNFi, whether primary or secondary nonresponse, have limited treatment options given the limited effectiveness of other TNFi or vedolizumab in these patients. The onset of action with vedolizumab is not viewed as rapid, which may limit its use in patients suffering from moderately to severely active flare and therefore in need of rapid relief. In addition, the induction benefit of vedolizumab appears to be mostly in patients who had not previously failed TNFi agents.

Colectomy is generally considered last resort and is indicated only for refractory disease unresponsive to medical therapies, intolerable medication side effects and complications such as uncontrolled gastrointestinal (GI) bleeding, perforation and dysplasia/carcinoma. Colectomy can have a negative impact on QoL and is associated with common, short term and long term complications.

Clinical rationale

There is a significant unmet need in patients with moderately to severely active UC who have previously failed corticosteroids, AZA/6-MP, or biologics such as TNFi. Importantly, there is no single current therapeutic option that offers fast onset of action, strong induction and maintenance efficacy, as well as efficacy in the most difficult to treat patient population. The gastroenterology field is in need of a treatment that offers an advance from 5-ASA, is not a steroid or biological DMARD, and is not an injection. Tofacitinib has the potential to provide a major contribution to patient care by offering a significant clinical benefit over existing treatment options for patients with moderately to severely active UC.

Guidance

The TGA did not have a pre-submission meeting with the sponsor in respect of this application. The following European adopted guideline (referred to as the 'Adopted Guideline') was principally used in the clinical report:

- EMA Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis.[2]

Notwithstanding the following draft consultation/guideline, cited by the sponsor for some *post-hoc* analyses, may not yet have been accepted by the Committee for Medicinal Products for Human Use (CHMP), and the efficacy data provided in this submission dossier precedes this document, this evaluation will consider the submitted data in relation to this draft document to assess whether study design and methodologies are consistent across documents.

- EMA Draft guideline on the development of new medicinal products for the treatment of Ulcerative Colitis.[3]

Contents of the clinical dossier

The dossier documented a development program of dose-finding, pivotal and one long-term clinical trial relating to the proposed extension of indication. However, pharmacology data was limited to a single population pharmacokinetic (PopPK) analysis.

The submission contained the following clinical information:

[3] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Draft guideline on the development of new medicinal products for the treatment of Ulcerative Colitis, consultation end: 31 January 2017, CHMP/EWP/18463/2006 – Rev 1.

Clinical dossier

- 1 PopPK analysis (PMAR-EQDD-A392i-sNDA-513).
- 1 pivotal Phase II dose-finding/induction study (Study A3921093).
- 2 pivotal Phase III efficacy/safety induction studies (Studies A3921094 and A3921095).
- 1 pivotal Phase III efficacy/safety maintenance study (Study A3921096).
- 1 other long-term efficacy/safety study (Study A3921139).
- Other reports:
  - 3 population modelling analysis reports (PMARs) for efficacy in patients with UC (PMAR-EQDD-A392i-sNDA-512; PMAR-EQDD-A392i-sNDA-680).
  - 2 PMARs for safety in patients with UC (PMAR-EQDD-A392i-sNDA-514 and PMAR safety meta-analysis for evaluating adverse events.)
  - 1 integrated summary of immunology.
  - 1 PopPK analysis in paediatric patients with UC (PMAR-EQDD-A392i-sNDA-694 and addendum).
  - Lipids and cardiovascular biomarker report derived from Study A3921078 (for chronic plaque psoriasis).
  - 1 Phase IIb efficacy/safety induction study in moderate to severe Crohn's disease (Study A3921083).
  - 1 Phase IIb efficacy/safety maintenance study in moderate to severe Crohn's disease (Study A3921084).
  - 2 PSURs for tofacitinib to cover 6 November 2015 to 5 November 2016.

Paediatric data

It was beyond the scope of this application to evaluate tofacitinib in paediatric populations. Tofacitinib is not currently approved for use in children below 18 years of age due to insufficient data on safety and efficacy in this population.

The sponsor submitted data to the US and the EU for the following paediatric age ranges for the proposed indication: adolescents (12 to 17 years) and children (2 to 11 years). The sponsor has an agreed Paediatric Investigation Plan in Europe (September 2017) and an agreed Pediatric Plan in the USA.

Good clinical practice

The studies that led to the proposed PI changes were all required to be conducted in accordance with ethical principles originating in or derived from the Declaration of Helsinki (World Medical Association 1996 and 2008) and in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were to be followed including the archiving of essential documents.

The clinical trials for induction and maintenance treatments of UC are claimed to have been conducted in accordance with the study protocol and be compliant with the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002). The final protocol, any amendments and informed consent documentation had to be reviewed and approved by the Institutional Review Board and/or Independent Ethics

Committee(s) at each investigational centre participating in the study. Investigators were required to inform their Institutional Review Board and/or Independent Ethics Committee(s) of study progress and occurrence of any serious and/or unexpected adverse events (AEs).

One major protocol deviation noted across all three pivotal Phase III studies could have major implications for study conduct and validity. Many subjects were incorrectly stratified into remission, or not in remission, at Baseline, and then randomised: 15 subjects in Study A3921094; 39 subjects in Study A3921095 and 202 (34.1%) subjects in Study A3921096. This error was not realised in time to take corrective measures. The sponsor did not provide further supporting documentation to demonstrate that efficacy would not be affected by inclusion, or exclusion, of these incorrectly stratified subjects, such as sensitivity analyses.

Pharmacokinetics

Studies providing pharmacokinetic data

No new PK studies were submitted in this application.

Evaluator's conclusions on pharmacokinetics

PK characteristics of tofacitinib are well established in RA.

The sponsor provided one PopPK analysis, based on sparse PK sample data from one Phase II study and three Phase III studies in its clinical development program for UC. PK of tofacitinib in a moderate to severe UC population was generally consistent with PK of tofacitinib from the sponsor's RA clinical development program. Notwithstanding these findings the Adopted Guideline [2] advises the following be considered when designing studies for treatment of UC for locally-acting medicinal products:

> 'For locally acting products, distribution studies are necessary. It is important that locally acting products for oral intake reach the entire colon, including the rectum. The influence of concomitant diarrhoea on distribution should be studied as well. Depending on the mechanism of action, effects of mucosal inflammation on drug absorption should be addressed.'

Since no additional PK studies were submitted in this application for the target population, the recommended approach to designing studies with an oral medicine that has a local action did not appear to be undertaken, nor did the sponsor provide adequate justification for deviation from the Adopted Guideline.[2]

In respect of the PopPK analysis, the sponsor's overall interpretation of the analyses is generally acceptable. However, the following observations are made: the effect of 'extent of disease' was not assessed as there was > 10% missing data, so an effect cannot be excluded. Furthermore, since 519 (7.2%) tofacitinib PK samples were excluded from the PopPK analysis due to 'significant data collection errors', the possibility of compromised GCP and conduct of the studies across the UC clinical development program needs to be considered.

Pharmacodynamics

Studies providing pharmacodynamic data

No new pharmacodynamic (PD) studies were provided for evaluation in this submission.

Evaluator's conclusions on pharmacodynamics

The sponsor did not provide new PD trial data for its proposed use of tofacitinib in moderately to severely active UC, or propose to include PD data for UC in its PI. Instead the sponsor provided published literature in support of the JAK/STAT pathway for immune-mediated inflammatory conditions. While the published literature provided in this application does provide some support for tofacitinib in inflammatory bowel diseases (IBD), it is insufficient for a new proposed indication, which should ideally be supported by well controlled trials of the active compound in the proposed indication, and with well-defined PD endpoints.

According to the Adopted Guideline,[2] PD properties of the therapeutic agent should provide an indication of when clinical remission is likely to occur that is, assist in establishing the appropriate duration of an induction study for instance. Given the primary site of action of tofacitinib in RA are within swollen joints, it is expected that the PD for UC, where the site of action is principally the colorectal mucosa, would be considerably different. Furthermore, PD properties of the investigational product may assist with the prediction of AEs and drug-drug interactions.

The sponsor did not explain why PD studies were not conducted for the proposed indication, nor provided adequate justification for deviation from the Adopted Guideline.[2]

Dosage selection for the pivotal studies

Selection of the 10 mg BID dose of tofacitinib for the pivotal Phase III induction studies (Studies A3921094 and A3921095) was based on efficacy data from Study A3921063, a Phase II, dose-ranging (0.5 mg to 15 mg), 8 week induction study in patients with moderately to severely active UC. This dose regimen was also based on the safety profile of tofacitinib characterised in UC patients in Study A3921063, as well as experience with this dose regimen in RA patients. Study A3921063 commenced with 10 mg and 15 mg tofacitinib treatment arms, but the latter strength was removed approximately 6 months after study commencement.

The primary objective in Study A3921063 was to demonstrate efficacy of tofacitinib in inducing a clinical response in subjects with moderate to severe UC. Induction of clinical remission in this population was a secondary objective. Remission was not an endpoint. Model predicted clinical remission rate (difference from placebo) in the 10 mg BID and 15 mg BID dose groups were 34.3% (90% confidence interval (CI): 23.4%, 45.3%) and 37.2% (90% CI: 25.3%, 49.0%), respectively, which indicated a marginal increase in efficacy at doses greater than 10 mg BID.

Dose selection for the maintenance study (Study A3921096), which enrolled subjects who achieved a clinical response at Week 8 from one of the Phase III induction studies, was also based on the dose response data from Study A3921063. The 10 mg BID dose regimen was selected on the assumption maintenance effect will be achieved at doses not higher than doses for achieving the induction effect. Inclusion of tofacitinib 5 mg BID in Study A3921063 allows for evaluation of a lower maintenance dose, while keeping the Phase III program to an appropriate program size. The RA program also supported the use of a tofacitinib 5 mg BID treatment arm.

Evaluator's conclusions on dose finding for the pivotal studies

The doses of tofacitinib studied in Study A3921063 were 0.5 mg, 3 mg, 10 mg and 15 mg. A tofacitinib 5 mg treatment arm was neither included in Study A3921063 nor estimated or extrapolated from the dose response model. Hence, an effect on induction using a tofacitinib 5 mg BID treatment regimen remains unknown. Also, the minimum effective

dose that will provide an acceptable level of remission in the target population remains unknown. This gap in knowledge may affect treatment selection.

Given the marginal increase in efficacy observed from tofacitinib 15 mg BID treatment compared with 10 mg treatment, it is unclear why 15 mg treatment was included in the Phase III induction studies. Especially since the initial report for Study A3921063 was available prior to commencement of the Phase III induction studies.

Notwithstanding that induction regimens for the treatment of moderate to severe UC in adults generally require higher induction or loading doses than maintenance regimens, the administration of a near maximal efficacious dose of tofacitinib to all participants has to be balanced against the AE profile of the active compound. The use of a lower dose regimen than 10 mg BID tofacitinib, say 5 mg for instance, would have provided assurance that the 10 mg BID regimen was optimal to induce clinical remission/remission, as well as provide comparative safety data between the different active treatment arms. Given the TGA's recent safety concerns over tofacitinib 10 mg BID treatment, the Phase III induction studies would not be expected to directly address those safety concerns, in the absence of an active comparator group.

The use of tofacitinib 5 mg BID treatment in the maintenance study (Study A3921096), while appearing a reasonable choice, is not directly supported from the dose response model employed in Study A3921063.

Efficacy

Studies providing efficacy data

- Study A3921094: a multicentre, randomised, double blind, placebo controlled, parallel group study of oral CP-690,550 (tofacitinib) as an induction therapy in subjects with moderate to severe ulcerative colitis (induction).
- Study A3921095: a multicentre, randomised, double blind, placebo controlled, parallel group study of oral CP-690,550 as an induction therapy in subjects with moderate to severe ulcerative colitis (induction).
- Study A3921096: a multicentre, randomised, double blind, placebo controlled, parallel-group study of oral CP-690,550 as a maintenance therapy in subjects with ulcerative colitis (maintenance).
- Study A3921063: a randomised, double blind, placebo controlled, parallel group, multicentre study to investigate the safety and efficacy of CP-690,550 in subjects with moderate to severe ulcerative colitis (dose-ranging/induction).
- Study A3921139: interim clinical study report: a multi-centre, open label study of CP-690,550 in subjects with moderate to severe ulcerative colitis (long-term extension).

Evaluator's conclusions on efficacy

Induction

Overall, the study design of the pivotal Phase III induction studies is acceptable and consistent with the Adopted Guideline.[2] However, some significant deviations occurred, which were not adequately addressed by the sponsor.

The primary and secondary objectives were achieved and statistically significant and clinically meaningful results obtained. Tofacitinib 10 mg BID treatment was effective in inducing remission with a pooled placebo adjusted rate of 11.6% (numbers needed to

treat (NNT) = 9), with an onset of action observed after 2 weeks of treatment. For the key secondary endpoint of mucosal healing at Week 8, the pooled placebo adjusted treatment effect for tofacitinib 10 mg was 16.3% (NNT = 6) and pooled placebo adjusted treatment effect for clinical response was 26.8% (NNT = 4).

The result of the primary efficacy analysis was supported by results from sensitivity analyses of the primary efficacy endpoint, as well as results from analyses of the secondary and exploratory efficacy endpoints. In subgroup analyses, the magnitude of treatment effect was similar, irrespective of prior UC treatment failures (oral corticosteroids, immunosuppressants, TNFi).

Clinical efficacy of tofacitinib 10 mg BID in induction was accompanied by improved quality of life based on the Inflammatory Bowel Disease Questionnaire, Short Form-36, Euro Quality of Life 5 Dimensions and Work Productivity and Activity Impairment.

However, lack of demonstration of a minimum effective induction dose has implications for the dosing regimen, and there are outstanding issues in regards to study conduct/GCP, which are the subject of the clinical questions to sponsor.

Maintenance

Both tofacitinib dose regimens achieved statistically significant and clinically meaningful pooled placebo adjusted rates of remission at Week 52 (primary efficacy endpoint) that is, 23.2% (NNT = 4) for tofacitinib 5 mg BID treatment and 29.5% (NNT = 3) for tofacitinib 10 mg BID treatment. This result was supported by the sensitivity analyses of the primary efficacy endpoint.

Similarly, both tofacitinib dose regimens achieved statistically significant and clinically meaningful pooled placebo-adjusted rates of maintenance of remission at Week 52 (key secondary efficacy endpoint) that is, 36.0% (NNT = 3) for tofacitinib 5 mg BID treatment and 46.2% (NNT = 2) for tofacitinib 10 mg BID treatment, and supported the findings from the primary efficacy analysis.

The apparent dose response treatment effect observed, which favoured (that is, greater effect) the tofacitinib 10 mg dose regimen over the tofacitinib 5 mg dose regimen, was consistent across the other secondary and exploratory efficacy endpoints investigated. In TNFi failure subjects, tofacitinib 10 mg BID also had greater observed maintenance efficacy than 5 mg BID at Week 52, with differences ranging from 9.7 to 16.7% across the primary and key secondary endpoints. Furthermore, the observed treatment effect was larger for secondary TNFi failures than primary TNFi failures for the primary and key secondary endpoints of remission and mucosal healing in both the individual and pooled studies.

Clinical efficacy of tofacitinib 10 mg BID was accompanied by maintenance of improvements in quality of life based on Inflammatory Bowel Disease Questionnaire, Short Form-36, Euro Quality of Life 5 Dimensions and Work Productivity and Activity Impairment.

There was no primary efficacy analysis in the long term extension Study (A3921139). However, the analyses of the secondary binary efficacy endpoints provide supportive evidence of continued maintenance of effect of tofacitinib treatments for at least 12 months. There were no meaningful differences in treatment effect between the tofacitinib dose regimens. Subjects that appeared to achieve the most benefit were those subjects who entered the open label study with Baseline remission from the maintenance study. In this subpopulation, maintenance of efficacy was observed for up to 24 months (74%), irrespective of tofacitinib dose.

The evidence provided in this submission supports a maintenance dose of tofacitinib 5 mg BID. Given that a reasonable proportion of subjects with prior TNFi failure achieved additional benefit from a tofacitinib 10 mg dose regimen, it would not be unreasonable to

offer this population a higher maintenance dose regimen (that is, tofacitinib 10 mg BID), if tolerated.

Additional efficacy analyses not specified in the study protocols or statistical analysis plans

The sponsor provided results for the induction studies and for the maintenance study, which were not specified in the study protocols or statistical analysis plans. These additional analyses were undertaken based on Food and Drug Administration (FDA) recommendations following a meeting on 2 June 2016. These analyses are claimed to be consistent with the relevant guidelines.[3] The Physician Global Assessment component of the total Mayo score;[4] was excluded from the analyses, on the basis it was no longer of primary interest.

The following endpoints were analysed (based on endoscopic central read findings; full analysis set) in the pivotal Phase III induction studies: modified remission at Week 8; modified symptomatic remission at Week 8; modified partial Mayo score at Weeks 2, 4, and 8. In addition, remission at Week 8 with Mayo stool frequency and rectal bleeding subscores derived from worst daily diary score was analysed.

In the maintenance study (Study A3921096), the following endpoints were analysed (based on endoscopic central read findings; full analysis set):Modified remission at Week 52; modified symptomatic remission at Week 52; and remission at Week 52 with Mayo stool frequency and rectal bleeding subscores derived from worst daily diary score.

The results from the modified induction and maintenance analyses are consistent with the primary efficacy analysis results for induction and maintenance treatment provided in the body of this report.

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

Nil.

Pivotal and/or main efficacy studies

Safety was assessed in the following pivotal efficacy studies:

- Study A3921094
- Study A3921095
- Study A3921096

Since the Phase III induction studies (Studies A3921094 and A3921095) are identical in study design and methodologies these studies have been assessed together in efficacy analyses of the clinical report. Hence, they will be reviewed together in this safety assessment with any significant difference/s in either study result identified separately.

Across all the 5 clinical trials for UC evaluated in this report, all AE assessments (including assessment of causality) were assessed by the investigator at each study visit (and unplanned if warranted) and up to 28 days post last study dose. The investigator was required to actively pursue each AE (spontaneous from subject or determined by

[4] The Mayo score assesses the severity of ulcerative colitis. It comprises four components, each with a score of 0 to 3; stool frequency, rectal bleeding, mucosal appearance at endoscopy and physician rating of disease activity. The higher the score (maximum 12 points) the more severe the ulcerative colitis.

investigator) and determine whether it satisfied the criteria for a serious adverse event (SAE) and notify the sponsor (and local regulator) accordingly, and follow up AEs as determined by the protocol and the sponsor. AEs were coded as per the Medical Dictionary for Regulatory Activities (Medical Dictionary for Regulatory Activities (MedDRA), Version 18.0).

- General AEs: number of AEs, subjects with AEs, subjects with SAEs, subjects with severe AEs, subjects discontinued due to AEs, subjects with dose reduced or temporary discontinuation due to AEs. Incidence and severity of AEs presented;
- AEs of particular interest: infections (including serious infections, opportunistic infections (OIs), herpes zoster (HZ) and tuberculosis (TB)); malignancies (excluding non-melanoma skin cancer (NMSC)); major adverse cardiovascular events (MACE); hepatic injury cases (including events adjudicated to be Hy's law cases and potential drug-induced liver injury (DILI) cases); GI perforation; interstitial lung disease (ILD); select hematologic events (anaemia, neutropenia, lymphopenia); AEs of renal impairment and AEs of creatine phosphokinase (CPK) elevation and rhabdomyolysis. Incidence of adjudicated safety events presented;
- Laboratory tests: haematology, clinical chemistry and lipids (high density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, cholesterol/HDL ratio, LDL/HDL ratio and triglycerides). Test results assessed from Baseline to study endpoint and presented as incidence and severity of laboratory abnormality.
- Other safety variables: electrocardiogram (ECG), vital signs and clinical examination. Incidence of vital sign abnormalities and changes from Baseline in vital signs; incidence of clinically significant changes in physical examination from Baseline; and incidence of ECG abnormalities.

In the Phase II and Phase III induction studies (duration 8 to 9 weeks), AEs were presented as proportions. In addition to AE proportions, *post-hoc* (that is, exploratory) incidence rates (IR) of AEs of special interest were also analysed in the maintenance and long-term extension studies to assess duration of exposure (in 6 month intervals) to assigned treatment (tofacitinib or placebo). IR rates are standardised to subjects with events per 100 patient-years (PY), provided there are sufficient numbers (> 12) of subjects to evaluate change over time.

Other studies

Other efficacy studies

- Study A3921139 (long term extension, referred to as Cohort 2 (P3 Maintenance) by the sponsor)

Studies with evaluable safety data: dose finding and pharmacology

- Study A3921063 (dose ranging/induction)

Patient exposure

Table 3: Exposure to tofacitinib and comparators to assigned treatment in clinical studies

Study type/ indication	Controlled studies				Uncontrolled studies	Total tofacitinib
	Tofacitinib 5 mg	Tofacitinib 10 mg	Tofacitinib 15 mg	Placebo	Tofacitinib 5 and 10 mg	
Dose ranging/ induction (A3921063)	0	33	49	48	0	194*
Induction of remission						
• Pivotal • A3921094 • A3921095	0 0	476 429	16 6	122 112	0 0	614 547
Subtotal Induction	**0**	**938**	**71**	**282**	**0**	**1355***
Maintenance of clinical response or remission						
Pivotal (A3921096)	198	196	0	198	0	592
Other **(A3921139)	0	0	0	0	156 and 758	914
Subtotal Maintenance/ long term	**198**	**196**	**0**	**198**	**914**	**1506**
Total	**198**	**1134**	**71**	**480**	**914**	**2861***

* Includes 64 subjects who received 0.5 mg (n = 31) tofacitinib and 3 mg (n = 33) tofacitinib in Study A3921063. ** Dose adjustments were allowed after 8 weeks of study treatment

In the combined clinical studies of the UC clinical development program, 1157 subjects received at least 1 dose of tofacitinib 5 mg BID or 10 mg BID, with 762 subjects exposed to tofacitinib for at least 6 months, and 653 subjects exposed for at least 12 months.

In total, the UC program encompassed 1613 patient years of exposure to tofacitinib (Table 4), with up to 4.4 years of tofacitinib treatment.

Table 4: Exposure of tofacitinib across the five clinical trials in the UC clinical development program by duration and predominant dose (5 mg or 10 mg)

Duration of Treatment	Tofacitinib All (N = 1157)	Predominant Dose 5 mg BID (N = 186)	Predominant Dose 10 mg BID (N = 971)
At least 1 month	1112	186	926
At least 3 months	918	184	734
At least 6 months	762	174	588
At least 12 months	653	147	506
At least 18 months	557	129	428
At least 24 months	359	87	272
At least 30 months	201	52	149
At least 36 months	93	23	70
At least 42 months	22	7	15
Mean (SD) (days)	509.1 (389.8)	709.9 (337.3)	470.6 (387.6)
Median (days)	514	710	427
Range (min, max) (days)	1-1606	52-1606	1-1504
Total PY	1612.8	361.5	1251.2

Safety issues with the potential for major regulatory impact

Adverse events of special interest

Infection adverse effects

Induction

In Study A3921094, more subjects in the tofacitinib 10 mg BID treatment group experienced infection AEs (23.3%, n = 111) compared with placebo treated subjects (15.6%, n = 19). No placebo subject experienced a serious infection, severe AE or discontinued due to infection AEs. In contrast 6 (1.3%) tofacitinib 10 mg treated subjects had SAEs, 3 (0.6%) had severe AEs and 3 (0.6%) discontinued the study permanently due to infection related AEs.

Of the 6 serious infections, 2 subjects experienced severe cellulitis and *C. difficile* infection, post treatment; 3 subjects discontinued the study due to anal abscess, severe febrile infection and pneumonia; and 1 subject continued the study with a severe otitis externa infection.

Treatment related infection AEs occurred in 9.7% (n = 46) of tofacitinib treated subjects compared with 4.9% (n = 6) of placebo treated subjects. Two (0.4%) tofacitinib 10 mg treated subjects had SAEs, 1 (0.2%) had severe febrile infection and 2 (0.4%; febrile infection and pneumonia) discontinued the study permanently due to infection related AEs.

In the tofacitinib 15 mg treated group, 1 (16.7%) subject experienced an infection AE (vulvovaginal candidiasis), but no subject had an infection related SAE, severe AE or discontinued due to an infection related AE.

In Study A3921095, more subjects in the tofacitinib 10 mg BID treatment group experienced infection AEs (78 subjects, 18.2%) compared with placebo (17 subjects, 15.2%). One subject (0.2%) in the tofacitinib 10 mg BID group experienced an infection SAE, 1 subject had a severe AE and 1 subject discontinued due to an infection related AE, compared with none in each corresponding category for subjects in the placebo group.

The most frequent (≥ 2% in either group) infection AEs were nasopharyngitis (tofacitinib 10 mg BID, 4.9%; placebo, 3.6%). There were 2 AEs of HZ in the tofacitinib 10 BID group and none in the placebo group.

More subjects in the tofacitinib 10 mg BID treatment group experienced treated related infection AEs (33 subjects, 7.7%) compared with placebo (6 subjects, 5.4%). In the tofacitinib treated group 1 (0.2%) subject each had one SAE (furuncle), one severe AE (pharyngitis) and 1 infection related AE that led to permanent discontinuation (furuncle) from the study.

In the tofacitinib 15 mg treated group, 6 (37.5%) subjects experienced infection AEs, but no subject had an infection-related SAE, severe AE or discontinued due to an infection related AE.

Maintenance

In Study 3921096, more subjects in the tofacitinib 5 mg BID group (71 subjects, 35.9%) and tofacitinib 10 mg BID group (78 subjects, 39.8%) experienced infection AEs compared with the placebo group (48 subjects, 24.2%). Infections that were SAEs, severe AEs and infection related AEs that led to study discontinuation were infrequently reported across all groups.

Severe infection AEs were reported in 2 subjects in the tofacitinib 5 mg BID treatment group (1 subject with influenza and pneumonia; 1 subject with peritonsillar abscess and tonsillitis), 3 subjects in the tofacitinib 10 mg BID treatment group (bacterial diarrhoea, gastroenteritis, and influenza) and none in the placebo group.

The most frequent infection AEs were nasopharyngitis (tofacitinib 5 mg BID: 9.6%; tofacitinib 10 mg BID: 13.8%; placebo: 5.6%), upper respiratory tract infection (URTI) (tofacitinib 5 mg BID: 6.6%; tofacitinib 10 mg BID: 6.1%; placebo: 3.5%), and gastroenteritis (tofacitinib 5 mg BID: 3.0%; tofacitinib 10 mg BID: 4.1%; placebo: 2.5%).

In the tofacitinib 5 mg BID group, 33 subjects (16.7%) had treatment related infection AEs and 1 subject (0.5%) had a treatment related infection SAE. In the tofacitinib 10 mg BID group, 41 subjects (20.9%) had treatment related infection AEs and 1 subject (0.5%) had a treatment related infection SAE. In the placebo group, 23 subjects (11.6%) had treatment related infection AEs and 2 subjects (1.0%) had treatment related infection SAEs. Two subjects each in the tofacitinib 5 mg BID group (1 with peritonsillar abscess and tonsillitis; 1 with influenza and pneumonia) and in the tofacitinib 10 mg BID group (bacterial diarrhoea, influenza) had a treatment related severe infection. Three subjects discontinued from study treatment (1 in each treatment group) due to treatment related infections, and 6 subjects (4 in tofacitinib 10 mg BID group; 1 each from placebo group and the tofacitinib 5 mg BID group) had their study drug temporarily discontinued due to a treatment related infection.

Serious infection AEs were reported by 2 subjects (1.0%) in the tofacitinib 5 mg BID group (peritonsillar abscess, urinary tract infection), 1 subject (0.5%) in the tofacitinib 10 mg BID group (bacterial diarrhoea), and 2 subjects (1.0%) in the placebo group (diverticulitis, subcutaneous abscess).

Other studies

In Study 3921063, System Organ Class (SOC) 'Infections and Infestations' accounted for the second greatest number of subjects reported AEs: placebo: 14.6%, 25.8%, 9.1%, 27.3% and 6.1%. Of the infections, nasopharyngitis accounted for the highest incidence: placebo 2.1%, 6.5%, 3.0%, 3.0%, and 2.0%. Two subjects in the tofacitinib 10 mg treatment group experienced at least 1 infection SAE (severe postoperative abscess and anal abscess, leading to discontinuation), but neither was considered treatment related.

In Study 3921139, 62 subjects (39.7%) in the tofacitinib 5 mg BID group and 317 subjects (41.8%) in the tofacitinib 10 mg BID group experienced infection AEs. Four subjects (2.6%) in the tofacitinib 5 mg BID group and 14 subjects (1.8%) in the tofacitinib 10 mg BID group experienced an infection SAE (serious infection). Few subjects reported severe

infection AEs or discontinued the study from infection AEs, and these were generally consistent between tofacitinib treatments.

Incidence of infection treatment emergent adverse events (TEAE) over time (2 months, 1 year, and 2 years) and age-group (< 65 and ≥ 65 years) were generally consistent between tofacitinib treatments. While infection AEs were similar between tofacitinib treatments for those who received baseline corticosteroids, the only SAEs, severe AEs and discontinuations from infection AEs occurred in the tofacitinib 10 mg treatment group. However, incidence of infection AEs more than doubled between 2 months and 12 months of treatment in either tofacitinib treatment group that is, tofacitinib 5 mg incidence of infection AEs within 2 months was 16.1%, within 1 year 36.7% and within 2 years 41.4% compared with tofacitinib 10 mg treatment group that is, incidence of infection AEs within 2 months was 15.4%, within 1 year 34.0% and within 2 years 39.7%.

The most frequent infection AEs for the tofacitinib 5 mg BID and tofacitinib 10 mg BID groups were nasopharyngitis (11.5% and 14.5%, respectively), URTI (4.5% and 7.0%, respectively), influenza (6.4% and 4.4%, respectively), HZ (4.5% and 4.1%, respectively), and gastroenteritis (2.6% and 4.1%, respectively). Appendicitis (reported in 1 subject in the tofacitinib 5 mg BID group and 2 subjects in the tofacitinib 10 mg BID group) and nasopharyngitis (reported in 2 subjects in the tofacitinib 10 mg BID group) were the only severe infections reported in more than 1 subject in either treatment group.

In the tofacitinib 5 mg BID group, 28 subjects (17.9%) had treatment related infection AEs and 1 subject (0.6%) had a treatment related infection SAE. In the tofacitinib 10 mg BID group, 154 subjects (20.3%) had treatment-related infection AEs and 6 subjects (0.8%) had a treatment related infection SAE. Six subjects in the tofacitinib 10 mg BID group had a severe treatment related infection (arthritis bacterial, atypical pneumonia, HZ, nasopharyngitis (2 events), and post procedural sepsis). Eight subjects discontinued due to treatment related infections (1 in the tofacitinib 5 mg BID group and 7 in the tofacitinib 10 mg BID group).

Herpes zoster adverse effects

In Study A3921094, there were 3 (0.6%) HZ cases in the tofacitinib 10 mg BID group and 1 (0.8%) in the placebo group, 2 were considered related to study drug (and 1 to viral infection) and also adjudicated as OIs. The single case of HZ in the placebo group was also considered study drug related. No cases of HZ were severe or recorded as SAEs. In Study A3921095, there were 2 (0.5%) subjects with HZ in the tofacitinib 10 mg BID group (0.5%), compared with none in the placebo group. Both events were considered study drug related, and of these was adjudicated as an OI based on multidermatomal involvement. Neither cases were severe, a SAE and no case discontinued the study due to a HZ infection.

In Study A3921096, the proportion of observed cases of HZ increased in a dose dependent manner, which achieved statistical significance for tofacitinib 10 mg treatment compared with placebo treatment (p = 0.0053;Table 5).

Table 5: Incidence of herpes zoster TEAEs by SOC and Preferred Term (PT) for Study A3921096 (safety analysis set)

Tier-1 TEAEs[a]	Placebo (N = 198)		Tofacitinib 5 mg BID (N = 198)			Tofacitinib 10 mg BID (N = 196)			
	n (%)	n (%)	Risk Difference[b]	95% CI[c]	p-value[c]	n (%)	Risk Difference[b]	95% CI[c]	p-value[c]
Infections and Infestations									
Herpes zoster	1 (0.5)	2 (1.0)	0.505	-1.871, 3.148	0.6827	10 (5.1)	4.597	1.439, 8.674	0.0053
Herpes zoster cutaneous disseminated	0	1 (0.5)	0.505	-1.434, 2.782	0.5295	0	N/A	N/A	N/A

No case of HZ was severe, a SAE or discontinued from the study due to HZ infection.

In Study 3921063, there were 2 cases of treatment related HZ in tofacitinib treated subjects: 1 (3.2%) for 0.5 mg treatment and 1 (3.0%) for 10 mg treatment.

In Study A3921139, treatment emergent HZ infections occurred with similar incidence in both tofacitinib treatment groups (Table 6).

Table 6: Incidence of treatment-emergent herpes zoster adverse events, all causalities

	Tofacitinib 5 mg BID (N = 156)	Tofacitinib 10 mg BID (N = 758)	Total (N = 914)
Number (%) of Subjects With AEs by SOC and PT			
Infections and Infestations	7 (4.5)	33 (4.4)	40 (4.4)
Herpes zoster	7 (4.5)	31 (4.1)	38 (4.2)
Herpes zoster disseminated (diffuse rash)	0	1 (0.1)	1 (0.1)
Ophthalmic herpes zoster	0	2 (0.3)	2 (0.2)
Total PT events	7	34	41

In the tofacitinib 10 mg BID group, 1 subject had a treatment emergent HZ SAE, 1 had severe HZ infection and 2 subjects discontinued due to TEAEs of HZ, and 9 other subjects temporarily discontinued due to a HZ infection.

Adjudicated events

To help assess specific safety events in the tofacitinib program, adjudication committees were established to harmonise and standardise selected safety event assessment. These committees included a Cardiovascular Endpoint Adjudication Committee (CV-EAC), Malignancy Adjudication Committee (MAC), Opportunistic Infection Review Committee (OIRC), Hepatic Event Review Committee (HERC), Gastrointestinal Perforation Review Committee (GIRPC) and an Interstitial Lung Disease Review Committee (ILDRC).

Cardiovascular

In Study A3921094, 2 subjects in the tofacitinib 10 mg BID treatment group experienced SAEs adjudicated as meeting criteria by the CV-EAC, but neither was considered related to study drug (1 acute coronary syndrome and 1 case of aortic dissection that led to death).

In Study A3921095, 1 subject in the tofacitinib 10 mg BID treatment group experienced 2 AEs adjudicated as meeting criteria by the CV-EAC and considered study drug related: 1 SAE of cardiac failure congestive and 1 mild AE of oedema peripheral.

No cases were reported in Study A3921063.

In Study A3921096, 2 subjects who received tofacitinib treatment had cardiovascular events adjudicated as meeting CV-EAC criteria. Only 1 was considered as study drug related: SAE of haemorrhagic stroke on tofacitinib 10 mg BID treatment. A SAE of myocardial infarction with tofacitinib 5 mg treatment was considered not study drug related.

In Study A3921139, 2 subjects in the tofacitinib 5 mg BID group had AEs adjudicated as meeting criteria by the CV-EAC (cardiovascular), neither was considered study drug related (1 subject had two SAEs that is, angina pectoris and cardiac failure; and 1 non serious mild dyspnoea).

Malignancy

In Study A3921094, one subject in the tofacitinib 10 mg BID treatment group experienced an AE of squamous cell carcinoma (SCC) that was adjudicated as a malignancy event by the MAC and considered possibly study drug related. In Study A3921095, one subject in the tofacitinib 10 mg BID treatment group experienced an AE of basal cell carcinoma (BCC) that was adjudicated as malignancy by the MAC, which was considered study drug related.

In Study A3921096, 3 subjects in the tofacitinib 10 mg BID group and 2 subjects in the placebo group experienced AEs adjudicated as malignancy events by the MAC. In the placebo group 1 case of invasive ductal carcinoma of the breast was considered unrelated to study drug while 1 cases of BCC was assessed as study drug related. In the tofacitinib 10 mg treatment group 1 case of BCC was not considered study drug related and 2 cases of SCC were considered study drug related.

No cases of malignancy were reported in Study A3921063.

In Study A3921139, the MAC confirmed 15 subjects had malignant events: 1 tofacitinib 5 mg; 14 tofacitinib 10 mg. Malignancy, excluding NMSC, was confirmed in 9 subjects, all in the tofacitinib 10 mg BID group.

Of the 9 subjects in the tofacitinib 10 mg BID group with confirmed malignancy, excluding NMSC, 3 subjects died during the study: 1 confirmed case each of hepatic angiosarcoma; acute myeloid leukaemia (AML) and cholangiocarcinoma.

For the other 6 cases who received tofacitinib 10 mg treatment: 1 case had confirmed Epstein–Barr virus (EBV)-associated lymphoma considered study drug related; 1 case of moderate cutaneous leiomyosarcoma (study drug related); 1 case of study related moderate essential thrombocythaemia; 1 case of study drug related renal cell carcinoma and 2 cases of non-study drug related malignancies (1 case of severe cervical dysplasia and 1 case of severe adenocarcinoma of colon).

Of the 6 subjects with NMSC events, 1 subject in the tofacitinib 5 mg BID group had BCC unrelated to study drug and 4 subjects in the tofacitinib 10 mg BID group had drug-related events (2 BCC, 2 SCC) and 1 subject had 2 SCC events adjudicated as unrelated to study drug.

Hepatic injury

In Study A3921094, HERC adjudicated that none of the 4 subjects who had a hepatic injury related AE following tofacitinib 10 mg BID treatment was study drug related. One placebo subject with aspartate transaminase (AST)/alanine transaminase (ALT) elevation ≥ 5 times upper limit normal (ULN) was adjudicated as possible DILI and another with probable DILI. None of these cases were reported as SAEs, and no event was adjudicated as a Hy's law[5] case in either treatment group.

In Study A3921095, HERC did not consider 2 hepatic injury events (AST/ALT elevation ≥ 5 times ULN) listed for tofacitinib treatment as study drug related. The placebo treated subject with a probable DILI assessment withdrew from the study due to insufficient clinical response. None of these cases was an SAE or adjudicated as a Hy's law case.[5]

In Study A3921096, 1 subject in the tofacitinib 10 mg BID treatment group had mild increases in ALT, AST, alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT), which were adjudicated as 'possible' DILI by HERC. No event was adjudicated as a Hy's law case.[5]

No hepatic injury events were reported in Study A3921063.

In Study A3921139, 5 subjects in the tofacitinib 10 mg BID group had adjudicated hepatic injury events. Two cases were assessed as possible DILI, but neither was considered study drug related. None of the events met the criteria for a Hy's law case.[5]

Opportunistic infections

In Study A3921094, two subjects in the tofacitinib 10 mg BID treatment group experienced events adjudicated by the OIRC as opportunistic infections (both HZ). Neither event was reported as a SAE or serious infection. Only 1 was considered related to study

[5] ALT or AST > = 3 times ULN and total bilirubin > = 2 times ULN and ALP < = 2 times ULN

drug (HZ that affected 2 adjacent dermatomes). One case of HZ that affected possibly 3 non-adjacent dermatomes was not considered drug related (but related to a viral infection).

In Study A3921095, two subjects in the tofacitinib 10 mg BID treatment group experienced treatment-related events that were adjudicated by the OIRC as OIs (HZ and cytomegalovirus (CMV) infection). Neither event was an SAE or serious infections.

No OIs were reported in Study A3921063.

In Study A3921096, 8of 13 (61.5%) cases of HZ infection were adjudicated as OIs and were all considered related to study drug: 1 in placebo, 3 in tofacitinib 5 mg and 4 in tofacitinib 10 mg groups, respectively.

In Study A3921139, 13 subjects were adjudicated by the OIRC as OIs and 12 considered study drug related: Ten subjects experienced HZ infection events (2 (1.3%) in the tofacitinib 5 mg BID group and 8 (1.1%) in the tofacitinib 10 mg BID group); an SAE of CMV hepatitis with tofacitinib 5 mg treatment and an SAE of histoplasmosis with tofacitinib 10 mg treatment. 1 AE of pulmonary mycosis with tofacitinib 5 mg treatment was not considered study drug related.

Gastrointestinal perforation

In the Phase III studies, there were 3 events adjudicated as GI perforations by the GIPRC. Of these, 2 were considered study drug related (anal abscess in Study A3921094 receiving tofacitinib 10 mg treatment) and (GI perforation in Study A3921096 receiving placebo treatment). One subject in the tofacitinib 10 mg group had a non-study drug related intestinal perforation.

Three events in Study A3921139 were adjudicated as GI perforations by the GIPRC. 1 event was considered study-related (GI perforation and EBV associated lymphoma receiving tofacitinib 10 mg treatment) and 2 events considered not study drug related (appendicitis in tofacitinib 5 mg group and pilonidal cyst requiring antibiotics and abscess drainage in tofacitinib 10 mg group).

Interstitial lung disease

There were no adjudicated events of ILD during studies A3921094, A3921095, A3921096, A3921063 and A3921139.

Liver function and liver toxicity

Pivotal and/or main efficacy studies

Across the induction studies, the proportions of subjects with abnormalities in each multiple of the ULN (≥ 1; ≥ 2; ≥ 3) were no higher in the tofacitinib 10 mg BID group than the placebo group for ALT and AST. No potential Hy's law case was identified.[5]

In Study A3921094, differences from placebo for adjusted mean changes were statistically significant for at every time point (Weeks 2, 4 and 8) for ALP. One subject (0.8%) in the placebo group met criteria for 2 sequential AST or ALT elevations ≥ 3 times ULN as well as for 2 sequential AST or ALT elevations ≥ 5 times ULN.

In Study A3921095, differences from placebo for adjusted mean changes were statistically significant for at every time point (Weeks 2, 4 and 8) for AST and ALP. No subject met the discontinuation criteria for liver function test (LFT) abnormalities.

In Study A3921096, increases in mean ALT and mean AST levels were observed throughout the study for both tofacitinib treatment groups compared with placebo. Incidence of ALT, AST and bilirubin values as multiples of the ULN generally demonstrated a dose-response relationship for each liver function tests (Table 7). Generally the higher the tofacitinib dose the higher the proportion of subjects with more elevated levels.

Table 7: Incidence of liver function test (ALT, AST, total bilirubin) values as multiples of the ULN, safety analysis set (Study A3921096)

	Tofacitinib 5 mg BID (N = 198) n (%)	Tofacitinib 10 mg BID (N = 196) n (%)	Placebo (N = 198) n (%)
ALT			
≥1 × ULN	30 (15.2)	37 (18.9)	17 (8.6)
≥2 × ULN	5 (2.5)	7 (3.6)	0 (0.0)
≥3 × ULN	0 (0.0)	2 (1.0)	0 (0.0)
AST			
≥1 × ULN	26 (13.1)	34 (17.3)	12 (6.1)
≥2 × ULN	3 (1.5)	5 (2.6)	2 (1.0)
≥3 × ULN	1 (0.5)	3 (1.5)	1 (0.5)
Total bilirubin			
≥1 × ULN	24 (12.1)	30 (15.3)	15 (7.6)
≥2 × ULN	3 (1.5)	4 (2.0)	3 (1.5)
≥3 × ULN	1 (0.5)	0 (0.0)	0 (0.0)

Difference from placebo in adjusted mean change from Baseline was statistically significantly greater for tofacitinib 10 mg BID treatment for ALT, AST and ALP at every time point (from Week 4 to Week 52). In contrast, 5 mg tofacitinib BID treatment demonstrated statistically significantly greater differences to placebo BID treatment at most time points to Week 16 for ALT, AST and ALP. There were no appreciable differences noted during the study between treatments for GGT and total bilirubin.

One (0.5%) subject in the tofacitinib 10 mg BID group met criteria for 2 sequential AST or ALT elevations ≥ 3 times ULN. Events of elevated liver enzymes (ALT, AST, ALP, and GGT) were reported and study drug withdrawn. There were no potential Hy's law cases.[5]

Other studies

In Study A3921063, without regard to baseline abnormality, there appeared to be a dose-related trend for elevated GGT levels > 3.0 times ULN: 1 (2.1%) case for placebo, 1(3.0%) case for tofacitinib 10 mg and 3 (6.1%) cases for tofacitinib 15 mg treatment. One subject in the tofacitinib 10 mg treatment group had AST and ALT levels between 2 to 3 times ULN and another subject in the tofacitinib 15 mg treatment group had total bilirubin between 1.5 to 2 times ULN. There were no AST or ALT > 3 times ULN or total bilirubin > 2 times ULN in tofacitinib treated subjects. No subject met the discontinuation criteria for LFT abnormalities or a Hy's law[5] case.

In Study A3921139, there were increases from baseline mean values in both treatments for ALT (7.444 for tofacitinib 5 mg and 8.324 for tofacitinib 10 mg) and AST (7.500 for tofacitinib 5 mg and 7.986 for tofacitinib 10 mg). The same trend was observed for GGT to Month 21. There were no appreciable effects on total bilirubin or ALP values over 24 months treatment.

The proportions of subjects who met abnormality criteria for total bilirubin, indirect bilirubin, ALT, AST, GGT, and lactate dehydrogenase were low and similar in both tofacitinib treatment groups. No subjects were in the abnormal range for ALP in either treatment group.

Three (0.4%) subjects in the tofacitinib 10 mg BID group had 2 sequential AST or ALT values of at least 3 times ULN and therefore met the protocol criteria for discontinuation for LFT abnormalities. For subjects with baseline values within the normal range, 1 subject met potential Hy's law[5] case in the tofacitinib 10 mg BID group (Subject [information redacted]). However, this event was determined not to be a confirmed Hy's Law case and was instead attributed by the HERC to cholangiocarcinoma.

Renal function and renal toxicity

Most subjects who experienced an increase in serum creatinine from Baseline experienced the lowest category of change from Baseline that is, > 10 to ≤ 33% increase, with a few experiencing the more severe categories (> 33 to ≤ 50% increase and > 50% increase). In the latter, most cases occurred in the maintenance study (Study A3921096) and the long-term extension study (Study A3921139). No AEs were reported involving serum creatinine, blood urea nitrogen, and uric acid or creatinine clearance abnormalities in any study. No subject met the criteria for study discontinuation for serum creatinine abnormalities.

Other clinical chemistry

Pivotal and/or main efficacy studies

Absolute neutrophil count

In both Phase III induction studies there were no meaningful differences in the mean change from Baseline between tofacitinib 10 mg and placebo treatments.

In Study A3921094, at Week 8, 14 tofacitinib treated subjects had neutropaenia (10 (2.3%) with absolute neutrophil count (ANC) 1.5 to < 2, 2 (0.5%) with ANC 1 to < 1.5 and 2 (0.5%) with ANC 0.5 to < 1) and 1 (0.9%) placebo treated subject (ANC 1 to < 1.5). In Study A3921095, at Week 8, 12 tofacitinib treated subjects had neutropaenia (9 (2.3%) with ANC 1.5 to < 2 and 3 (0.8%) with ANC 1 to < 1.5 and 5 placebo treated subjects had neutropaenia (4 (4.1%) with ANC 1.5 to < 2 and 1 (1.0%) with ANC 1 to < 1.5. No subject in any treatment arm, across studies, had an ANC < 0.5 and no subject met the discontinuation criteria.

In Study A3921096, overall mean change from Baseline to study end (Week 52) revealed no meaningful changes between treatments. There were no meaningful differences in the rate of abnormalities in ANC between treatment groups. Most neutropaenia cases had ANCs (10^3/mm^3) of 1.5 to < 2, or of 1 to < 1.5. No cases of ANC < 0.5 were observed in any treatment group and no subject met the discontinuation criteria.

In Study A3921063, without regard to baseline abnormality, there was a dose-related trend for neutrophilia (total neutrophils < 0.8 times lower limit of normal (LLN)) for tofacitinib treated subjects: 1 (2.1%) for placebo; 0 (0.0%) for 0.5 mg; 1 (3.0%) for 3 mg; 2 (6.1%) for 10 mg and 3 (6.1%) for 15 mg, respectively.

In Study A3921139, overall, there were minimal changes from Baseline over time for the tofacitinib 5 mg BID group. In contrast, there was a decreasing trend from Baseline over time for the tofacitinib 10 mg BID group: mean ANC at Baseline was 5.93 compared with 4.44 at Month 24 (change from Baseline: -1.257). Without regard to baseline abnormality, each tofacitinib treatment demonstrated neutropenia (total neutrophils < 0.8 times LLN) in 5.1% of subjects.

Most neutropaenia cases had ANCs (10^3/mm^3) of 1.5 to < 2, or ANCs of 1 to < 1.5. No cases of ANC < 0.5 were observed in either treatment group over 24 months. One subject in the tofacitinib 10 mg BID group died from AML and met the discontinuation criteria.

Lymphocyte count

In both the Phase III induction studies, there were no meaningful differences in the mean change from Baseline between tofacitinib 10 mg and placebo treatments, or lymphocyte abnormalities.

In Study A3921094, there were two cases (0.4%) of mild lymphopaenia in the tofacitinib 10 mg BID treatment group. One (0.2%) subject met criteria for discontinuation.

In Study A3921095, difference from placebo in adjusted mean change from Baseline was statistically significantly greater for tofacitinib 10 mg treatment at Weeks 4 and 8 for

lymphocytes (absolute). At Week 8 the relative difference between tofacitinib and placebo treatments in subjects with an ANC 0.5 to < 1.5 was higher in the tofacitinib group (38.2% versus 25.8%, respectively). In contrast, in Study A3921094, 36.9% tofacitinib treated subjects had ANC 0.5 to < 1.5 compared with 37.6% for placebo treated subjects.

In Study A3921096, mean changes from Baseline in absolute lymphocyte count (ALC) values (in $10^3/mm^3$) were greater for both tofacitinib treatments compared with placebo: -0.285 for tofacitinib 5 mg; -0.464 for tofacitinib 10 mg versus -0.091 for placebo. From Week 32 to Week 52, tofacitinib 10 mg produced a relatively greater reduction in ALC than tofacitinib 5 mg treated subjects. Analysis of changes from Baseline demonstrated that treatment effects were statistically significantly different from placebo for both tofacitinib groups at Weeks 24 and 52.

Lymphocyte abnormalities (without regard to baseline abnormality) were similar between tofacitinib treatments and greater than placebo treated subjects: tofacitinib 5 mg (15.2%), tofacitinib 10 mg (14.9%), placebo (5.6%).

In all treatment groups, most subjects with lymphocyte abnormalities had values in the ALC ≥ 2, 1.5 to < 2, and 0.5 to < 1.5 categories. No subject in any treatment group had ALC < 0.5 at Week 52. At Week 52, proportionately more tofacitinib treated subjects were in category 0.5 to < 1.5 than categories ALC ≥ 2 and 1.5 to < 2 that is; those subjects who recorded lymphopenia had relatively more severe lymphopenia than placebo treated subjects.

Other studies

In Study A3921063, without regard to Baseline abnormality, there were low lymphocyte counts (< 0.8 times LLN) across all treatment groups: 7 (14.9%) for placebo; 2 (6.5%) for 0.5 mg; 2 (6.1%) for 3 mg; 3 (9.1%) for 10 mg and 4 (8.2%) for 15 mg, respectively.

In Study A3921139, overall mean values in change from Baseline revealed a generally decreasing trend in ALC over time, for both tofacitinib treatments, and which suggest a dose related trend.

Lymphocyte abnormalities (without regard to baseline abnormality) were higher in the tofacitinib 10 mg BID group than the tofacitinib 5 mg BID group for 'absolute lymphocytes' (< 0.8 times LLN) that is, 22.0% versus 17.3%, respectively and for 'lymphocytes' (%) that is, 34.2% versus 21.8%, respectively. At Baseline, 1 subject in the 10 mg group had ALC < 0.5. During the first 24 months of this open label study there was a gradual lowering of ALC over time. Six subjects in the tofacitinib 10 mg BID group met the discontinuation criteria.

Haematology and haematological toxicity

Abnormally low haemoglobin (< 0.8 times LLN) and other red cell indices occurred infrequently with no dose related trends observed. In Study A3921094, there were 3 subjects with AEs of haemoglobin decreased (1 each in tofacitinib 10 mg and placebo treatment groups). In Study A3921095, 1 (0.2%) subject had moderate haemoglobin decreased in the tofacitinib 10 mg BID group. No case was severe.

Most subjects with decreased haemoglobin (g/dL) were categorised as a change from Baseline of -1 to ≥ -2 g/dL in all treatment groups. Change from Baseline haemoglobin of ≤ -3 or value of ≤ 7 occurred rarely.

Anaemia was reported in 17 subjects in Study A3921094: 11 (2.3%) subjects in the tofacitinib 10 mg BID group and 6 (4.9%) subjects in the placebo group. Fourteen subjects had anaemia in Study A3921095: 11 (2.6%) in the tofacitinib 10 mg BID group and 3 (2.7%) in the placebo group. Fifteen subjects had anaemia in Study A3921096: 8 (4.0%) subjects in the tofacitinib 5 mg BID group, 4 (2.0%) subjects in the tofacitinib 10 mg BID group, and 3 (1.5%) subjects in the placebo group. One case of severe anaemia was

reported in Study A3921096 in the tofacitinib 10 mg treatment group (and met the criteria for study discontinuation).

Six subjects in the Phase III induction program had two sequential haemoglobin values < 8.0 g/dL or a decrease from Baseline of > 30% and therefore met the criteria for discontinuation: 1 (0.8%) subject in the placebo group in Study A3921094 and 5 (1.2%) subjects in Study A3921095 (all in the tofacitinib 10 mg BID treatment group). In the long-term extension study (A3921139), 6 subjects in the tofacitinib 10 mg BID group met the discontinuation criteria compared with none in the tofacitinib 5 mg BID group.

In Study A3921139, without regard to baseline abnormality, tofacitinib 10 mg BID had higher incidence of haemoglobin (and haematocrit) abnormalities than tofacitinib 5 mg that is, 11.7% versus 1.3%, respectively (and 5.9% versus 0.6%, respectively for haematocrit abnormalities). Tofacitinib 10 mg subjects generally had higher incidence of more severe categories of haemoglobin reductions than tofacitinib 5 mg subjects over the first 24 months of the study.

Other laboratory tests

Lipids

Pivotal and/or main efficacy studies

In Study A3921094, mean percent increases from Baseline at Week 8 in total cholesterol, LDL, and HDL were greater for the tofacitinib 10 mg BID treatment group (total cholesterol 16.4%; LDL 16.3%; HDL 25.2%) compared with placebo (total cholesterol 4.2%; LDL 6.4%; HDL 4.5%).

Differences from placebo in adjusted mean changes from Baseline were significant at Week 4 and Week 8 for total cholesterol (both $p < 0.0001$); HDL (both $p < 0.0001$); LDL ($p = 0.0002$ and $p < 0.0001$, respectively); Total cholesterol/HDL ratio ($p< 0.0001$ and $p = 0.0008$, respectively); and LDL/HDL ratio ($p < 0.0001$ and $p = 0.0001$). Differences for triglycerides were not statistically significant at Week 4 or Week 8.

Abnormal baseline total cholesterol (> 1.3 times ULN), LDL (> 1.2 times ULN), and HDL (< 0.8 times LLN) occurred in 15.9%, 42.5% and 1.8%, respectively, of the tofacitinib 10 mg BID group, and in 0.0%, 9.1% and 0.0%, respectively, of the placebo group. In all subjects, regardless of baseline value, a greater proportion of subjects in the tofacitinib 10 mg BID group (17.0%) had total cholesterol values > 1.3 times ULN, compared with placebo group (9.0%). LDL cholesterol values > 1.2 times ULN occurred more in the tofacitinib 10 mg BID group (19.3%) compared with placebo group (9.0%). Triglyceride values > 1.3 times ULN occurred in 3.2% of the tofacitinib 10 mg BID group, compared with 0.8% of the placebo group. HDL cholesterol values < 0.8 times LLN occurred in 1.3% of the tofacitinib 10 mg BID group, compared with 1.6% of the placebo group. More subjects were taking lipid lowering agents at Baseline in the tofacitinib 10 mg BID treatment group (7.14%) compared with placebo (4.92%).

In Study A3921095, mean increases from Baseline at Week 8 in total cholesterol, LDL, and HDL were greater for the tofacitinib 10 mg BID treatment group (total cholesterol 19.2%; LDL 20.9%; HDL 25.5%) compared with placebo (total cholesterol 4.5%; LDL 5.6%; HDL 5.5%). The mean changes from Baseline at Week 8 for the cholesterol/HDL ratio and for the LDL/HDL ratio were -3.0% and -0.9%, respectively, for the tofacitinib 10 mg BID group, and 0.7% and 1.8%, respectively, for the placebo group.

Differences from placebo in adjusted mean changes from Baseline were significant at Week 4 and Week 8 for: Total cholesterol ($p < 0.0001$) and HDL ($p < 0.0001$); and LDL ($p < 0.0001$), but not triglycerides.

Abnormal baseline total cholesterol (> 1.3 times ULN), LDL (> 1.2 times ULN), and HDL (< 0.8 times LLN) occurred in 15.5%, 44.4%, and 0.0%, respectively, of the tofacitinib

10 mg BID group, and in 2.9%, 4.8%, and 0.0%, respectively, of the placebo group. In all subjects, regardless of baseline value, a greater proportion of subjects in the tofacitinib 10 mg BID group (17.2%) had total cholesterol values > 1.3 times ULN, compared with placebo group (5.4%). LDL cholesterol values > 1.2 times ULN occurred more in the tofacitinib 10 mg BID group (21.7%) compared with placebo group (10.8%). Triglyceride values > 1.3 times ULN occurred in 2.8% of the tofacitinib 10 mg BID group, compared with 1.8% of the placebo group. HDL cholesterol values < 0.8 times LLN occurred in 1.7% of the tofacitinib 10 mg BID group, compared with 0.9% of the placebo group.

Similar proportions of subjects were taking lipid-lowering agents at Baseline in the tofacitinib 10 mg BID treatment group (5.83%) compared with placebo (4.46%).

In Study A3921096, in all subjects, regardless of baseline value, a greater proportion of subjects in the tofacitinib 5 mg BID group (27.3%) and the tofacitinib 10 mg BID group (22.6%) had total cholesterol values > 1.3 times ULN, compared with placebo group (8.1%). LDL cholesterol values > 1.2 times ULN occurred more in the tofacitinib 5 mg BID group (31.3%) and the tofacitinib 10 mg BID group (28.2%) compared with placebo group (18.7%). HDL cholesterol values < 0.8 times LLN occurred in 4.5% of the tofacitinib 5 mg BID group and 1.5% of the tofacitinib 10 mg BID group, compared with 6.1% of the placebo group. Triglyceride values > 1.3 times ULN occurred in 4.5% of the tofacitinib 5 mg BID group and 7.7% of the tofacitinib 10 mg BID group, compared with 3.5% of the placebo group.

More subjects were taking lipid lowering agents at Baseline in the placebo group (8.6%) compared to the tofacitinib 5 mg BID treatment group (6.1%) and the tofacitinib 10 mg BID treatment group (6.6%). During the double blind treatment period, addition of new lipid lowering agents occurred in 2 subjects (1.0%) in the tofacitinib 5 mg BID group, 6 subjects (3.1%) in the tofacitinib 10 mg BID group, and 1 subject (0.5%) in the placebo group.

Other studies

In Study A3921063, without regard to baseline abnormality, tofacitinib 10 mg and 15 mg treatments had observed elevated total cholesterol (> 1.3 times ULN), LDL cholesterol (> 1.2 times ULN) and triglycerides (> 1.3 times ULN) compared with placebo treatments: 8 (24.2%) versus 9 (18.4%) versus 5 (10.6%) for total cholesterol, respectively and 9 (27.3%) versus 9 (18.4%) versus 4 (8.5%)for LDL cholesterol, respectively and 2 (6.1%) versus 3 (6.1%) versus 0 (0.0%) for triglycerides, respectively.

There were dose related increases from Baseline to Week 8 in mean LDL and mean HDL across all dose groups. No subjects required initiation of lipid-lowering medication during the study. One subject on tofacitinib 10 mg experienced treatment-related dyslipidaemia.

In Study A3921139, total cholesterol, HDL cholesterol, LDL cholesterol, cholesterol/HDL cholesterol ratio and LDL cholesterol/HDL cholesterol ratio revealed overall small mean reductions over time for tofacitinib 5 mg treatment, whereas for each of these lipid parameters tofacitinib 10 mg treatment resulted in increasing trends from Baseline over time. Triglyceride values revealed overall increasing trends over time from the baseline values in the tofacitinib 5 mg BID group (mean change: 10.1%) and in the tofacitinib 10 mg BID group (mean change: 18.9%).

In all subjects, regardless of baseline value, a greater proportion of subjects had total cholesterol values > 1.3 times ULN in the tofacitinib 5 mg BID group (31.4%) than in the tofacitinib 10 mg BID group (22.3%). LDL cholesterol values > 1.2 times ULN occurred more in the tofacitinib 5 mg BID group (36.5%) than the tofacitinib 10 mg BID group (26.3%). Triglyceride values > 1.3 times ULN occurred more frequently in the tofacitinib 5 mg BID group (8.3%) than in the tofacitinib 10 mg BID group (3.2%). HDL cholesterol values < 0.8 times LLN were similar between groups, occurring in 1.9% of the tofacitinib 5 mg BID group and 2.7% of the tofacitinib 10 mg BID group.

A higher percentage of subjects were taking lipid lowering agents at Baseline in the tofacitinib 5 mg BID group (9.0%) compared to the tofacitinib 10 mg BID group (6.2%). Addition of new lipid lowering agents was reported in 1.9% of subjects in the tofacitinib 5 mg BID group and 4.2% in the tofacitinib 10 mg BID group. No subjects in the tofacitinib 5 mg BID group and 1.5% of subjects in the tofacitinib 10 mg BID group had dosages of lipid lowering agents increased during the treatment period.

Creatine phosphokinase

Pivotal and/or main efficacy studies

In Study A3921094, differences in adjusted mean change from Baseline in CPK compared with placebo were not statistically significant. A greater proportion of subjects (without regard to baseline abnormality) in the tofacitinib 10 mg BID group (9.5%) had CPK values > 2 times ULN, compared with the placebo group (1.6%).

Twelve (2.5%) subjects in the tofacitinib 10 mg BID treatment group had blood CPK increased, including 3 severe events, compared with no subjects in the placebo group. Two (0.4%) subjects in the tofacitinib 10 mg BID treatment group and 2 (1.6%) subjects in the placebo group experienced myalgia. There were no AEs of rhabdomyolysis or myopathy. One (0.2%) subject in the tofacitinib 10 mg BID group met the criteria for study discontinuation.

In Study A3921095, differences in adjusted mean change from Baseline in CPK compared with placebo were statistically significant at Week 8 ($p = 0.0006$).

Similar proportions of subjects in each treatment group had CPK values > 2 times ULN (tofacitinib 10 mg BID: 9.4%; placebo: 8.9%). Thirteen (3.0%) subjects in the tofacitinib 10 mg BID treatment group had blood CPK increased, compared with 3 (2.7%) subjects in the placebo group, including 1 case which was severe. Four (0.9%) subjects in the tofacitinib 10 mg BID treatment group experienced myalgia. No subject met the discontinuation criteria.

In Study A3921096, difference from placebo in adjusted mean change from Baseline was statistically significant for tofacitinib 10 mg treatment for CPK at Weeks 8, 16, 24, 32 and 52 and for tofacitinib 5 mg at Weeks 8, 24, 32 and 52. A greater proportion of subjects in the tofacitinib 5 mg BID group (18.7%) and the tofacitinib 10 mg BID group (27.7%) had CPK values > 2 times ULN, compared with the placebo group (7.1%), without regard to baseline abnormality.

Thirteen subjects in the tofacitinib 10 mg BID treatment group (6.6%) had blood CPK increased (including 1 severe), compared with 6 subjects in the tofacitinib 5 mg BID treatment group (3.0%) and 4 subjects in the placebo group (2.0%, 1 severe). Six subjects in the tofacitinib 5 mg BID treatment group (3.0%, 1 severe), 1 subject in the tofacitinib 10 mg BID treatment group (0.5%, mild), and 4 subjects in the placebo group (2.0%, 1 severe) experienced myalgia. One subject in the placebo group experienced mild rhabdomyolysis. No subject in the tofacitinib treatment group had rhabdomyolysis. There were no AEs of myopathy. Two subjects (1.0%) in the tofacitinib 10 mg BID group met the criteria for discontinuation.

Other studies

No CPK results were reported in Study A3921063. In Study A3921139, there was no notable median percent change from Baseline for subjects in the tofacitinib 5 mg BID group. In the tofacitinib 10 mg BID group an increase in median percent change from Baseline was observed at Month 1 and continued through Month 24 (89.3 percent change from Baseline). Incidence of CPK abnormalities without regard to baseline abnormality was similar between tofacitinib treatments. There were no AEs of rhabdomyolysis reported. Two subjects in the tofacitinib 5 mg BID group and 3 subjects in the tofacitinib 10 mg BID group met the discontinuation criteria.

Electrocardiograph findings and cardiovascular safety

Pivotal and/or main efficacy studies

Most subjects had no significant changes in ECG findings across the Phase III studies, irrespective of randomised treatment assignation. In Study A3921095, 1 subject in the tofacitinib 10 mg BID group had moderate left bundle branch block. In Study A3921094, for tofacitinib 10 mg treatment, 1 subject had mild extrasystole, 2 subjects had sinus tachycardia another had an AE of 'ECG abnormal' compared with placebo treatment in which 1 subject had sinus tachycardia and 1 subject had sinus bradycardia. In Study A3921096, 1 subject in the tofacitinib 10 mg BID group had a mild event of atrioventricular block first degree compared with 1 subject in the placebo group had a mild prolongation of the QT-interval (QT corrected 450 to < 480 ms).

Other studies

In Study A3921063, abnormal findings were not considered clinically significant. In Study A3921139, 1 subject in the tofacitinib 5 mg BID group reported mild sinus bradycardia. In the tofacitinib 10 mg BID group the following events were reported in 1 subject each with mild severity: arrhythmia, bundle branch block left, bundle branch block right, supraventricular extrasystoles and ventricular extrasystoles.; 2 subjects reported mild sinus bradycardia and 1 subject reported moderate sinus tachycardia.

Vital signs and clinical examination findings

Pivotal and/or main efficacy studies

Vital signs

The proportions of subjects meeting systolic blood pressure (BP), diastolic BP, and pulse rate criteria for potential clinical concern were low and similar across treatment groups in the Phase III studies. There were no AEs due to vital sign abnormalities that led to temporary discontinuation, dose reduction or to permanent study drug or study discontinuation.

Hypertension was reported in 6 (1.3%) subjects in Study A3921094 in the tofacitinib 10 mg treatment group (one case was severe) and 1 (0.8%) in the placebo treatment group. No event was a SAE. Hypertension was reported in 3 (0.7%) subjects in Study A3921095 in the tofacitinib 10 mg treatment group. One case was a SAE. In Study A3921096, hypertension was reported in 4 (2.0%) subjects in the tofacitinib 5 mg BID group, 4 (2.0%) subjects in the tofacitinib 10 mg BID group and 1 (0.5%) subject in the placebo group. No event was a SAE.

Orthostatic hypotension occurred in 1 subject in the tofacitinib 10 mg BID group (0.2%) in Study A3921094. Two (1.0%) subjects in the tofacitinib 10 mg BID group had events of body temperature increased in Study A3921096. No event was a SAE.

In Study A3921096, systolic BP increase ≥ 30 mm Hg occurred in 5.6% and 5.2% of subjects in the tofacitinib 5 mg BID and 10 mg BID groups, and in 3.1% of subjects in the placebo group. Diastolic BP increase ≥ 20 mm Hg occurred in 4.6% and 5.2% of subjects in the tofacitinib 5 mg BID and 10 mg BID groups, and in 2.1% subjects in the placebo group.

Clinical examination

In Studies A3921094, A3921095 and A3921096, at Baseline, there were no notable differences between treatment groups in the proportion of subjects with abnormal physical examination findings. The percentages of subjects with significant changes in physical examination findings were generally similar between treatment groups for the duration of each study.

Other studies

Vital signs

In Study A3921063, no vital sign values were considered clinically significant except subjects who received 15 mg tofacitinib BID treatment had markedly higher elevations in systolic BP ≥ 30 mm Hg than other treatment groups: 12.2% (n = 6) compared with 2.1 to 6.5% for placebo, tofacitinib 0.5 mg, 3 mg and 10 mg. Given the small numbers of cases these findings should be interpreted with caution.

In Study A3921139, the proportions of subjects meeting systolic BP criteria for potential clinical concern were lower in the tofacitinib 5 mg BID group than in the tofacitinib 10 mg BID group. Systolic BP increase ≥ 30 mm Hg occurred in 4.6% and 9.9% of subjects in the tofacitinib 5 mg BID and 10 mg BID groups, respectively. Systolic BP decrease ≥ 30 mm Hg occurred in 3.9% and 4.9% of subjects in the tofacitinib 5 mg BID and 10 mg BID groups, respectively. Systolic BP < 90 mm Hg occurred in similar proportions of subjects in the tofacitinib 5 mg BID (1.3%) and tofacitinib 10 mg BID (1.6%) groups.

Diastolic BP increase ≥ 20 mm Hg occurred in 4.6% and 12.4% of subjects in the tofacitinib 5 mg BID and 10 mg BID groups, respectively. Diastolic BP decrease ≥ 20 mm Hg occurred in 13.8% and 7.8% of subjects in the tofacitinib 5 mg BID and 10 mg BID groups, respectively. Diastolic BP < 50 mm Hg occurred 0.6% of subjects in the tofacitinib 5 mg BID group and 1.7% of subjects in the tofacitinib 10 mg BID group. The proportions of subjects meeting pulse rate criteria for potential clinical concern were low in both treatment groups.

Hypertension was reported in 2 (1.3%) subjects in the tofacitinib 5 mg BID and 9 (1.2%) subjects in the tofacitinib 10 mg BID group. Hypotension was reported in 1 (0.6%) subject in the tofacitinib 5 mg BID group and 2 (0.3%) subjects in the tofacitinib 10 mg BID group. No event was a SAE.

Two subjects in the tofacitinib 10 mg BID group had AEs due to vital sign abnormalities (hypertension, pyrexia) that led to temporary discontinuation or dose reduction. No subject had vital sign abnormalities that led to permanent study discontinuation.

Clinical examination

In Study A3921063, there were no notable differences between treatment groups in the proportion of subjects with abnormal physical examination findings. In Study A3921139, the proportion of subjects with abnormal findings was notably lower in the tofacitinib 5 mg BID group compared with the tofacitinib 10 mg BID group.

Serious skin reactions

No cases of photosensitivity, erythema multiforme, Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS) or toxic epidermal necrolysis have been reported in the UC clinical development program or listed in the approved PI.

Other safety issues

Safety in special populations

In the 'Precautions' section of the approved PI indicates that Asian populations may be at higher risk of experiencing AEs such as HZ infection, OIs, ILD, elevated transaminases and decreased white blood cell (WBC) counts. These effects are proposed to occur from an exaggerated PD effect to tofacitinib that is, higher exposure gives rise to higher clinical response, with subsequent higher rates of AEs (RA application PM-2012-00788-3-3).

Study A3921094 recruited 65 Japanese subjects and Study A3921095 recruited 58 Korean subjects into the Phase III induction program. The sponsor did not provide separate safety analyses of AEs of special interest in Asian populations, although 'Asian' was used as a

covariate in *post-hoc* modelling of AEs of special interest and was not identified as a predictor of serious infections. However, the number of Asian subjects with AEs of special interest was too small to draw meaningful conclusions. The Asian population should continue to be an identified safety concern in the risk management plan (RMP).

Safety related to drug-drug interactions and other interactions

No data were provided or discussion presented by the sponsor. In the absence of data, significant clinical drug-drug interactions with concomitant UC treatments cannot be excluded.

Post-marketing data

As of 5 November 2016, tofacitinib was approved in 51 countries and marketed in 37 countries. Following a negative opinion by the EMA's CHMP in 2013, the resubmitted application for treatment of RA in 2016 had the 5 mg tablet approved on 22 March 2017.

As of 5 November 2016, cumulatively, approximately 21,362 subjects have participated in tofacitinib sponsor-initiated clinical trials worldwide and 14,052 subjects exposed to tofacitinib. Cumulatively, there have been approximately 61,043 PY of exposure to tofacitinib from marketing experience.

The sponsor provided two 6 monthly Periodic Safety Update Reports (PSUR) in support of its application: PSUR 7, which covered the period 6 November 2015 to 5 May 2016 and PSUR 8, which covered the period 6 May 2016 to 5 November 2016. Since both PSURs preceded the application for registration of tofacitinib citrate in moderate to severe UC, safety data is mostly limited to tofacitinib usage in patients with RA.

- PSUR 7:
  - This makes reference to the TGA's decision to only register Xeljanz (tofacitinib citrate) 5 mg tablets, on 5 February 2015, based on safety concerns for the 10 mg BID regimen.
- PSUR 8:
  - Following a negative opinion by the FDA for an application of tofacitinib for the treatment of moderate-to-severe chronic plaque psoriasis (PsO) in October 2015, the sponsor withdrew all global applications for treatment of PsO in July 2016.; and
  - The signal 'increased risk of herpes zoster in the Korean population' was categorised as an important identified risk. This is captured in the approved Australian PI (along with Japanese population under 'Asian').

Ongoing safety signals include reduction in renal function (as reflected in decreased measured glomerular filtration rate and increased serum creatinine) and pancreatic ductal carcinoma.

Evaluator's conclusions on safety

No new safety signal was identified in the submission dossier for adults with moderate to severe ulcerative colitis, which evaluated subjects exposed with tofacitinib for up to 4.4 years duration.

Induction and maintenance treatment appeared to be generally well tolerated, with few severe or SAEs reported. Tofacitinib 10 mg treatment generally had higher incidence of AEs (treatment-emergent and treatment-related), SAEs, severe AEs and AEs that resulted in study discontinuation in maintenance and long-term open label treatments than tofacitinib 5 mg treatment. Since there were no tofacitinib 5 mg treatment arms in the

Phase III induction studies no similar comparison can be made, although it would seem reasonable to infer that the proportions of AEs would be less for tofacitinib 5 mg treatment (particularly as a comparison between the 5 mg and 10 mg doses for RA in the approved PI generally indicate similar or lower frequencies of AEs).

In general, the types of adverse events were consistent with those adverse events documented in the approved PI. In particular, tofacitinib treatment was associated with increases in serum LDL cholesterol, HDL cholesterol and CPK, and decreases in ALC.

Across studies, the most frequently occurring AEs (treatment emergent and treatment related) were consistently reported in the 'Infections and infestations' (often in a dose-response trend) and 'Gastrointestinal disorders' SOCs. The most common GI adverse event was ulcerative colitis. In the maintenance and long term open label extension study an inverse dose related trend was generally observed for UC, in which incidence became lower with increasing dose of tofacitinib treatment. This trend is most likely to reflect underlying disease progression than a treatment-related adverse effect.

GI perforations (including a revised definition that excluded fistulae and abscesses below the peritoneal reflection) occurred infrequently with tofacitinib treatment. Two of the 3 GI perforations reported across studies occurred in subjects at high risk for GI perforation. There appeared to be no evidence of dose- or time-dependency risk for GI perforation in the study population.

There were no malignancies (excluding NMSC) in either the tofacitinib 5 mg BID or tofacitinib 10 mg BID groups in the induction studies (Phase II and Phase III). Dose dependency for the risk of malignancies (excluding NMSC) with long-term tofacitinib treatment in UC patients cannot be excluded. Also a dose-dependency risk of NMSC cannot be ruled out based on the results of the maintenance study (A3921096) that is, there were no NMSC events in the tofacitinib 5 mg BID group, whereas the IR for tofacitinib 10 mg BID (1.91 out of 100 PY, 3 subjects) was higher than for placebo (0.97 out of 100 PY, 1 subject). There was no clustering of malignancies (excluding NMSC) into specific types of cancer. The higher ratio of SCC to BCC (estimated by sponsor as 7:6) suggests tofacitinib has an immunomodulatory effect, particularly as all SCC cases occurred with tofacitinib 10 mg treatment.

The data does not suggest an increasing risk of NMSC with longer duration of treatment with tofacitinib, but an effect cannot be ruled out until long-term experience with tofacitinib in an UC population is available. On this basis, malignancies, including NMSC, should remain as a safety concern in the RMP.

MACE occurred infrequently in tofacitinib-treated subjects. Based on medical history, 3 out of the 4 subjects with MACE had pre-existing cardiovascular risk factors. There was no evidence of dose-dependency or time-dependency risk of MACE. In addition, there were few clinically meaningful vital sign or ECG abnormalities (including hypertension and QT prolongation) that would increase cardiovascular risk. However, risk of cardiovascular (and cerebrovascular) risk is potentially raised in subjects who have an adverse lipid profile since tofacitinib has consistently demonstrated a dose-response relationship between tofacitinib exposure and raised levels LDL cholesterol and lowered levels of HDL cholesterol. Regular monitoring of patients receiving long-term use of tofacitinib, irrespective of treatment dose, would seem to be indicated, particularly for patients with co-morbidities that place them at higher risk of a cardiovascular or cerebrovascular event.

Three of the 4 reported deaths in the dossier were related to malignancies, although no cluster by type was observed, which would be more indicative of a treatment-related effect of tofacitinib exposure. One of these subjects had received 8 weeks of tofacitinib 15 mg BID induction treatment. The sponsor calculated the mortality rate as 0.12 out of 100 PY based on 2 deaths (occurred with 28 days of last dose) with a sensitivity analysis

of 0.24 out of 100 PY that includes all 4 deaths. These rates are not higher than expected for UC patients.

Infections generally occurred with the highest AE frequency across studies, although few serious infections were reported, and none resulted in death. The sponsor claims in the Summary of Clinical Safety that the only significant risk factor identified by multivariate analysis was body weight ≥ 90 kg.

Anaemia is a well-documented predicted AE of tofacitinib treatment and was reported across trials, although haemoglobin and other red cell indices were generally low, with no apparent dose-response trends observed.

There were very few hepatic injuries adjudicated to be possibly study drug related. Even though dose-related trends were generally observed across the studies for ALT, ALP and AST, no case of Hy's law was reported (except for one subject who died from a pulmonary embolism secondary to his cholangiocarcinoma, which resulted in elevated liver function parameters).

Opportunistic infections were infrequent. Most were limited to 1 or 2 adjacent dermatomes. Non-HZ OIs consisted of 1 event each of pulmonary cryptococcosis, pulmonary histoplasmosis and CMV hepatitis/CMV colitis. There were no deaths resulting from OIs. A *post-hoc* analysis of the maintenance study population suggested there was a dose-response relationship in risk of developing an OI: placebo treatment (0.97 out of 100 PY) versus tofacitinib 5 mg treatment (1.35 out of 100 PY) versus tofacitinib 10 mg treatment (2.60 out of 100 PY), although there was no clear time-dependency relationship observed for OI incidence with duration of tofacitinib exposure.

In the Summary of Clinical Safety, the sponsor states:

> '*The IR of OIs in the Tofacitinib All group in Cohort 3 (Phase II, Phase III long term extension Tofacitinib) was higher than those reported for the RA and PsO programs (all exposure*)'. The sponsor suggests the higher rate of OIs in an UC population '*may reflect a period effect associated with more frequent and more detailed reporting of herpes zoster OIs in the UC program resulting from greater understanding gained over time of the risk of herpes zoster during tofacitinib treatment'.*

While untested, the explanation provided by the sponsor appears to have merit, but an enhanced risk in an UC population cannot be ruled out until more long-term experience of tofacitinib in UC patients is available. On this basis, opportunistic infections, in particular herpes zoster OIs should remain a safety concern in the RMP.

In Study A3921096, the proportion of observed cases of HZ increased in a dose-dependent manner, which achieved statistical significance for tofacitinib 10 mg treatment compared with placebo treatment ($p = 0.0053$). The IR for herpes zoster (all) was numerically higher for tofacitinib 5 mg BID (2.05 out of 100 PY, 3 subjects) and tofacitinib 10 mg BID (6.64 out of 100 PY, 10 subjects) than for placebo (0.97 out of 100 PY, 1 subject), with the difference in IR in the tofacitinib 10 mg BID group versus placebo reaching statistical significance. This finding suggests dose dependency in the risk of developing herpes zoster. The sponsor claims no relationship to duration of exposure by comparing overall results versus maintenance results. No HZ (all) resulted in death.

The sponsor claims the IR of HZ (all) in the Tofacitinib All group in Cohort 3 (Phase II, Phase III long term extension Tofacitinib) was generally similar to those reported in the RA and PsO programs (all exposure) but higher than those reported for biologic agents in UC patients in external observational data.

Among subjects who had failed TNFi treatment, there were trends towards increased IRs of HZ (all) and NMSC in the tofacitinib 10 mg BID group in Cohort 2 (Phase III Maintenance), and increased IRs of HZ (all), NMSC and malignancies (excluding NMSC) in

the Tofacitinib All group in Cohort 3 (Phase II, Phase III long term extension Tofacitinib) when compared with the non-TNFi failure subgroup. In exploratory Cox regression analysis, the status of prior TNFi failure was found to be significantly associated with an increased risk of HZ and NMSC.

In the 71 subjects who received tofacitinib 15 mg BID as an 8 week induction treatment there was generally no significant safety findings, apart from the death of one subject from cholangiocarcinoma in which tofacitinib exposure was considered to have had a contributory effect.

A comparison of the proportions of adverse events listed in the approved PI for RA in the Phase III clinical trials (up to 3 months treatment) for the tofacitinib 10 mg BID dose regimen, revealed that the UC subjects in the Phase III induction program generally had higher proportions of most of the common AEs listed in the approved PI for RA. Notwithstanding the differences in study populations, design and duration of exposure, the following AEs consistently had higher proportions of AEs in UC subjects than RA subjects: anaemia; abdominal pain; nausea; pyrexia; nasopharyngitis, raised CPK; arthralgia and headache.

The safety findings observed during the UC program generally support the long-term use of tofacitinib 5 mg BID and 10 mg BID in adult patients with moderate-to-severe UC. However, the safety (and efficacy) of a tofacitinib 5 mg dose regimen in an acutely unwell population with moderate to severe disease remains unknown.

First round benefit-risk assessment

First round assessment of benefits

Table 8 summarises the assessment of benefits for Xeljanz (tofacitinib) for the proposed indication at the first round evaluation.

Table 8: First round assessment of benefits

Benefits	Strengths and Uncertainties
• A tofacitinib 10 mg BID regimen produces a clinically meaningful response (remission and mucosal healing) in an 8 week induction regimen in patients with moderately to severely active ulcerative colitis. A clinically meaningful response was noted as early as 2 weeks post-Baseline and persisted throughout the study duration. • Maintenance of response (including remission) was maintained for approximately one year with both tofacitinib 5 mg and 10 mg treatment regimens for the target population. This allows for some flexibility in dosing for example in patients who have documented poor response to TNFi treatment/s. • No new safety signal was identified in the submission dossier for tofacitinib in the target population	• The primary efficacy result (remission at Week 8) was supported by most of the sensitivity, subgroup, and secondary and exploratory efficacy analyses. • The optimal duration of induction treatment remains unknown as no pharmacodynamic studies were submitted in the submission dossier. • The lowest effective dose that may induce remission in the target population remains unknown. • The characteristics of non-responders to tofacitinib induction treatment remain unclear. • The primary efficacy result (proportion of subjects in remission at Week 52) was supported by most of the sensitivity, subgroup, and secondary and exploratory efficacy analyses. Also maintenance of effect was generally maintained for up to 12 months in a long term open label extension study (particularly for subjects who entered the open label study in remission from the maintenance study referred to as 'maintenance remitters'). • Due to long latency of some adverse events for example malignancies, any such association may not become apparent until exposure to tofacitinib becomes greater. In addition, rare (unpredictable) adverse events may also not become apparent until exposure of tofacitinib becomes greater.

First round assessment of risks

Table 9 summarises the assessment of risks of Xeljanz (tofacitinib) for the proposed indication at the first round evaluation.

Table 9: First round assessment of risks

Risks	Strengths and Uncertainties
• Administration of a tofacitinib 10 mg induction dose regimen may produce unacceptably higher incidence of adverse events of special interest and adverse events in general (including severe and serious adverse events) than a lower tofacitinib dose regimen. • While clinically meaningful efficacy results were obtained and sustained during maintenance treatments with both tofacitinib 5 mg and 10 mg regimens, and adverse events rates were generally higher with the tofacitinib 10 mg treatment regimen, development of serious adverse events (including death) and adverse events of special interest (such as malignancies) may become apparent in time with long term tofacitinib 5 mg treatment.	• Since there is no alternative tofacitinib dose regimen for induction treatment the 10 mg regimen may produce an unacceptably high number of adverse events in an acutely unwell population with ulcerative colitis. • Given the concerns raised by the TGA in a previous application for RA (that resulted in registration of just the tofacitinib 5 mg dose), non-inclusion of a lower induction regimen than tofacitinib 10 mg does not directly address the previously raised concerns. Furthermore, many of the concerns previously raised by the TGA in respect of RA were aligned with similar concerns by the EMA. In 2017, the EMA approved the use of tofacitinib 5 mg in RA (but not a tofacitinib 10 mg regimen). • In addition, tofacitinib global development programs have been ceased in Crohn's disease, kidney transplantation and, more recently, moderate to-severe chronic plaque PsO (2015; negative opinion from the FDA). The removal of the tofacitinib 15 mg treatment arm in the UC Phase III induction program adds weight to the global uncertainty around tofacitinib and what can be considered an acceptable dose as well as an acceptable level of risk. • Most of the adverse events of special interest are well documented, especially in the RA program and appear to be predictable/possibly related to systemic exposure. Hence, while more adverse events generally occurred with higher incidence with tofacitinib 10 mg treatment in the clinical trials reported in this submission, given the apparent PK/PD relationship of exposure to adverse events, longer duration with the tofacitinib 5 mg regimen will be expected to give rise to those predictable AEs with longer duration/exposure. • While the sponsor provided many detailed post-hoc analyses that generally appear to indicate there is no effect on AE type and duration of exposure, numbers of cases are too small to draw meaningful conclusions and such associations still remain plausible.

First round assessment of benefit-risk balance

The evaluator was not in a position to complete the assessment of benefit risk balance until a response to the questions raised in the first round evaluation had been received.

First round recommendation regarding authorisation

The evaluator was not in a position to recommend authorisation until a response to the questions raised in the first round evaluation had been received.

Clinical questions and second round evaluation

Efficacy

Question 1

Was the major protocol deviation 'Subject was randomized according to the wrong stratification' identified before or after each of the pivotal Phase III studies (Study A3921094, Study A3921095 and Study A3921096) was unblinded?

Please provide further details on how this deviation was identified, as well as how it occurred.

What proportion of subjects in the pivotal Phase III induction studies (A3921094 and A3921095) identified with the protocol deviation 'Subject was randomized according to the wrong stratification' were wrongly randomised on two separate occasions that is, at the end of their induction treatment Phase (Week 8) as well as their maintenance treatment Phase (at study Baseline)?

The sponsor is requested to provide an additional analysis in each study, of the primary efficacy endpoint, in which subjects who had the major deviation 'Subject was randomized according to the wrong stratification' are excluded from the primary efficacy analysis.

Sponsor's response: induction

The sponsor provided a detailed explanation on the process of stratification and how the interactive voice response system (IVRS) and the case report form (CRF) were reconciled during the induction studies, prior to database lock. The sponsor claimed that the data had been correctly reported in the CRFs and that errors were made during subject randomisation. Except, errors in stratification factors based on geographic region were set-up within the IVRS and hence not due to site data entry errors, but otherwise discovered and corrected.

When data from the CRF were compared with stratification data, overall percentages of subjects with errors reporting prior TNFi use, or Baseline corticosteroid use, were generally similar across treatment groups and across the induction studies, with all recorded values less than 5%. Two further subjects in Study A3921095, who both received tofacitinib 10 mg BID treatment, recorded stratification errors due to geographic region.

In the primary efficacy analyses, the sponsor claimed that potential errors in stratification factors were controlled for using data from the CRF for each stratification factor, instead of that entered by sites into the IVRS.

Analysis of remission at induction Week 8, excluding subjects with the major protocol deviation *'Subject was randomized according to the wrong stratification'*, are summarised in Table 10.

Table 10: Remission at Week 8 in Studies A3921094 and A3921095, excluding subjects with the major protocol deviation of 'subject was randomised according to the wrong stratification', full analysis set, non-responder imputation, central read

Study	Tofacitinib 10 mg BID N = 465 (A3921094) N = 399 (A3921095) n (%)	Placebo N = 118 (A3921094) N = 103 (A3921095) n (%)	Difference from Placebo (95% CI)[a]	P-value[b]
A3921094	86 (18.5)	10 (8.5)	10.0 (3.9, 16.2)	0.0094
A3921095	68 (17.0)	4 (3.9)	13.2 (7.9, 18.4)	0.0008

Source: 5.3.5.1 Regulatory response A3921094 Table 280a.1.1; A3921095 Table 280a.1.2.
Abbreviations: BID = twice a day; FAS = full analysis set; N = number of subjects in the analysis set; n = number of subjects meeting the endpoint criteria; NRI = non-responder imputation;
a. The 95% CI is based on the normal approximation for the difference in binomial proportions.
b. P-value based on Cochran-Mantel-Haenszel (CMH) chi-squared test stratified by prior treatment with anti-TNF, Corticosteroids use at baseline and geographic region.

Evaluation of response

The sponsor's response is generally acceptable. Omission of the major protocol deviation '*Subject was randomized according to the wrong stratification*', in either induction study, did not adversely affect the outcome from the primary efficacy analysis (remission at Week 8, central read, full analysis set, non-responder imputation) that is, the magnitude of effect (difference from placebo) and the statistical significance were retained:

- Study A3921094: Difference from placebo (95% CI): 10.3 (4.3, 16.3) p = 0.0070; and
- Study A3921095: Difference from placebo (95% CI): 13.0 (8.1, 17.9) p = 0.0005.

Hence, the major protocol deviation *'Subject was randomized according to the wrong stratification*' did not have an adverse effect on the primary efficacy analysis, in either induction study (Studies A3921094 and A3921095).

Sponsor's response: maintenance

In the maintenance study (Study A3921096), subjects were stratified at the time of randomisation according to treatment assignment from the induction studies, and the degree of clinical response that is, whether remission was achieved (Yes or No). The following explanation was provided to explain the high proportion of subjects in each treatment arm, who recorded the major protocol deviation *'Subject was randomized according to the wrong stratification':*

> As confirmation of remission status requires derivation of Mayo subscores from ICOPhone data and calculation of Mayo scores, which leads to programming complexity, as well as the real-time nature of the randomization process, the IVRS was not programmed to confirm the maintenance study Baseline remission status.
>
> As the Study A3921096 stratification factors included the induction study treatment assignment, all of the Study A3921096 stratification factors were blinded to both the sites and the sponsor while the induction studies were ongoing. Therefore, the stratification factors for remission status were only unblinded to the sponsor after the induction study closure. At this time, it was realized that a large percentage of subjects had been incorrectly stratified based on remission status at Study A3921096 Baseline. However, as all subjects had been randomized into Study A3921096 by that time, corrective actions could not be taken.

Table 11 was included in the sponsor's response and detailed the comparison between baseline remission status from the IVRS against programmatically derived binary endpoints, by treatment groups, and total maintenance population. Overall, the percentages of subjects with errors were similar across treatment groups (tofacitinib 5 mg

BID: 32.8%; tofacitinib 10 mg BID: 36.0%; placebo: 34.3%). Most errors were due to the sites responding in the IVRS that the subjects had achieved remission, whereas derivation based on the actual Study A3921096 baseline Mayo subscores showed the subjects had only achieved clinical response and not remission. These findings were consistent using local read endoscopic subscores.

Table 11: Summary of baseline remission status in the IVRS versus derived binary endpoints by treatment groups and overall population in maintenance Study A3921096 (full analysis set, central read)

Treatment Group Derived Binary Endpoint[a] at Study A3921096 Baseline	IVRS Remission, yes n (%)	IVRS Remission, no n (%)
Overall (N = 593)		
Remission, yes	173 (29.2)	**6 (1.0)**
Remission, no	**198 (33.4)**	216 (36.4)
Clinical response, yes, and remission, no	**192 (32.4)**	212 (35.8)
Clinical response, no	**6 (1.0)**	4 (0.7)
Tofacitinib 5 mg BID (N = 198)		
Remission, yes	62 (31.3)	**3 (1.5)**
Remission, no	**62 (31.3)**	71 (35.9)
Clinical response, yes, and remission, no	**58 (29.3)**	70 (35.4)
Clinical response, no	**4 (2.0)**	1 (0.5)
Tofacitinib 10 mg BID (N = 197)		
Remission, yes	52 (26.4)	**3 (1.5)**
Remission, no	**68 (34.5)**	74 (37.6)
Clinical response, yes, and remission, no	**67 (34.0)**	73 (37.1)
Clinical response, no	**1 (0.5)**	1 (0.5)
Placebo (N = 198)		
Remission, yes	59 (29.8)	**0 (0.0)**
Remission, no	**68 (34.3)**	71 (35.9)
Clinical response, yes, and remission, no	**67 (33.8)**	69 (34.8)
Clinical response, no	**1 (0.5)**	2 (1.0)

Source: 5.3.5.1 Regulatory response A3921096 Table 237a.42.1
Abbreviations: BID = twice a day; FAS = full analysis set; IVRS = interactive voice response system; n = number of subjects meeting the endpoint criteria; N = number of subjects in the Overall or individual treatment group and used as denominator in percentage calculation.
a. Efficacy binary endpoint is derived (separate from site assessment in IVRS) per the last non-missing measurements of Mayo subscores in the induction studies (A3921094 and A3921095)
Bold numbers indicate mismatches in the 2 databases.

In the primary efficacy analysis, the sponsor claimed that potential errors in stratification factors were controlled for using programmatically derived Study A3921096 Baseline remission status, instead of data entered by sites into the IVRS.

Analysis of remission at Week 52 in the maintenance study, excluding subjects with the major protocol deviation '*Subject was randomized according to the wrong stratification*', are summarised in Table 12.

Table 12: Remission at Week 52 in Study A3921096, excluding subjects with the major protocol deviation of 'subject was randomised according to the wrong stratification', full analysis set, non-responder imputation, central read

Treatment Group	N	n (%)	Difference from Placebo (95% CI)[a]	P-value[b]
Tofacitinib 5 mg BID	133	50 (37.6)	26.1 (16.3, 36.0)	<0.0001
Tofacitinib 10 mg BID	127	50 (39.4)	27.9 (17.8, 38.0)	<0.0001
Placebo	131	15 (11.5)		

Source: 5.3.5.1 Regulatory Response A3921096 Table 280a.1.3
Abbreviations: BID = twice a day; CI = confidence interval; FAS = full analysis set; N = number of subjects in the analysis set; n = number of subjects meeting the endpoint criteria; NRI = non-responder imputation.
a. The 95% CI is based on the normal approximation for the difference in binomial proportions.
b. P-value based on Cochran-Mantel-Haenszel (CMH) chi-squared test stratified by induction study treatment and baseline remission status.

Evaluation of response

The sponsor's response is generally acceptable, and it provides some assurance that the primary efficacy analysis was undertaken on the correct baseline remission status for each subject.

Omission of the protocol deviation '*Subject was randomized according to the wrong stratification'*, did not adversely affect the outcome from the primary efficacy analysis (remission at Week 52, by treatment group, central read, full analysis set, non-responder imputation) that is, the magnitude of effect (difference from placebo) and the statistical significance were retained:

- Tofacitinib 5 mg BID: Difference from placebo (95% CI): 23.2 (15.3, 31.2) $p < 0.0001$; and
- Tofacitinib 10 mg BID: Difference from placebo (95% CI): 29.5 (21.4, 37.6) $p < 0.0001$.

However, the relative treatment difference between tofacitinib 5 mg BID and tofacitinib 10 mg BID was reduced, after adjustment for placebo, from 6.3 in the primary efficacy analysis to 1.8 in the primary efficacy analysis after correction for the major protocol deviation '*Subject was randomized according to the wrong stratification'.*

Sponsor's response: Stratification errors across induction and maintenance studies

The sponsor claimed that it was not possible to mis-randomise subjects at both the end of induction (that is, at Week 8) and at the baseline of the maintenance study. Furthermore, across the induction and maintenance studies, eight subjects had stratification errors in both the induction and maintenance studies and a total of 248 subjects had stratification errors in either the induction or maintenance studies.

Evaluation of response

The evaluator acknowledges there was an error in the wording used in the clinical question. Randomisation at induction Baseline was intended, not Week 8, as initially documented. Notwithstanding this mistake, the sponsor did provide a satisfactory answer to the clinical question as it was intended.

Given only 8 subjects had stratification errors across the induction and maintenance studies, this number of subjects is not expected to adversely affect the results of the primary efficacy analyses in either the induction study or the maintenance study.

Summary of evaluation of response

The sponsor's response is generally acceptable. The derivation of errors in assigning stratification factors in both the induction studies (Studies A3921094 and A3921095) and

the maintenance study (Study A3921096) has been adequately explained, and the methods employed in the primary efficacy analyses to correct for such stratification errors also adequately described. Overall, assurance has been provided that the major protocol deviation '*Subject was randomized according to the wrong stratification'*, did not adversely affect the primary efficacy analysis in any of the induction studies or maintenance study.

While omission of those subjects with the major protocol deviation from the maintenance study (Study A3921096) reduced the placebo-adjusted difference between the tofacitinib 5 mg BID and tofacitinib 10 mg BID treatment arms from 6.3 to 1.8, both values are not clinically meaningful. Furthermore, given the proposed maintenance dose regimen is 5 mg BID, the effect of this major protocol deviation does not adversely affect the benefit-risk balance, which favours the 5 mg BID dosage regimen for maintenance treatment.

Since 248 subjects had stratification errors in either the induction or maintenance studies, this most probably reflects the problems inherent in conducting two sequential clinical trials, with a short period between cessation of one study and commencement of the second study. This is especially important when treatment assignation in the follow-on study requires specific information derived from the previous study, at the time of randomisation (baseline remission status in this application). As a result, the sponsor had to employ a programmatically derived method to determine baseline remission status for its maintenance study subjects. This is not ideal and assumes the program used to derive the remission status has both high precision and high reproducibility. The use of such computer programs has potential to introduce bias into the study design, which could affect the validity of the results.

If the adopted guideline[2] recommendation to allow for an adequate period between induction and maintenance studies had been more closely followed then most of the instances of the reported major protocol violation '*Subject was randomized according to the wrong stratification'* may have been avoided, with a concomitant reduction in the potential to introduce bias into the design from using a computer program to derive Baseline remission status.

Question 2

For what reason/s was the tofacitinib 15 mg treatment arm removed from the pivotal efficacy induction studies (Protocol Amendment 3 in Study A3921094; Protocol Amendment 2 in Study A3921095) on 30 November 2012? The sponsor is requested to provide a more detailed explanation than cited in the submission dossier, which infers the withdrawal of the tofacitinib 15 mg treatment arm was not on grounds of safety but few details were provided.

Sponsor's response

The 15 mg BID dose was removed via protocol amendments shortly after study start in 2012, based on feedback received in interactions with regulatory authorities around dosing for the RA indication at the time, and the complexity of developing a dose (15 mg BID) not included in the Phase III development programs for non-UC indications. The potential lack of clinical relevance of the small incremental increase in efficacy expected at 15 mg BID compared to 10 mg BID in UC patients, based on exposure-response analyses of efficacy data, was an additional consideration for this decision.

Evaluation of response

The sponsor's response was generally acceptable. However, the sponsor did not provide further information about what feedback it received from its interactions with regulatory authorities around RA dosing that prompted withdrawal of the 15 mg BID dose regimen, and subsequent study protocol amendments that required major changes to the sample size calculations and statistical power estimations, as well as the randomisation process in

each pivotal Phase III efficacy study. Such changes have potential to introduce bias into the study design and affect internal validity, as single factors and in combination.

In the absence of further specific information on what the *'feedback received in interactions with regulatory authorities around dosing for the RA indication at the time'* consisted, which gave rise to the withdrawal of the tofacitinib 15 mg BID treatment arm in the induction studies, an informed judgement about the appropriateness of withdrawing an active treatment arm approximately four to six months after commencement in each induction study cannot be fully made. Furthermore, this same statement was available in the submission dossier and the sponsor has therefore failed to *'provide a more detailed explanation than cited in the submission dossier'* as cited in the clinical question.

Question 3

The sponsor is requested to provide the results of the primary efficacy analysis (proportion of subjects in remission at Week 8) and the key secondary efficacy analysis (proportion of subjects with mucosal healing at Week 8) for each pivotal Phase III induction study that is, Study A3921094 and Study A3921095, by treatment group, extent of disease category (proctosigmoiditis; left-sided colitis; extensive/pancolitis) and disease severity category (Baseline total Mayo scores: < 8; 8 to 10; > 10).

Sponsor's response

The sponsor provided succinct tabulated data as requested for the primary efficacy endpoint (proportion of subjects in remission at Week 8) and the key secondary efficacy endpoint (proportion of subjects with mucosal healing at Week 8) by individual pivotal induction study, A3921094 and A3921095.

Evaluation of response

Extent of disease and disease severity will be considered separately.

Extent of Disease

No statistical separation or clinically meaningful benefit was demonstrated for the primary efficacy or secondary efficacy endpoints, in subjects who received tofacitinib 10 mg BID treatment for 8 weeks induction and who had predominantly proctosigmoiditis. These findings were consistent across the induction studies and the pooled analyses (Table 13).

Table 13: Remission and mucosal healing at Week 8 in induction Studies A3921094 and A3921095 and pooled results by baseline extent of disease, treatment difference from placebo and number needed to treat (full analysis set, non-responder imputation, central read)

Endpoint Subgroup	Induction Study	Treatment difference from placebo	Number need to treat
Remission			
Procosigmoiditis	A3921094	-2.6	No benefit
	A3921095	14.6	7 (NS)
	Pooled	5.4	19 (NS)
Left-sided colitis	A3921094	8.8	11 (NS)
	A3921095	15	7
	Pooled	12	8
Extensive colitis/pancolitis	A3921094	14.8	7
	A3921095	11	9
	Pooled	13.1	8
Mucosal Healing			
Procosigmoiditis	A3921094	7.5	13 (NS)
	A3921095	12.6	8 (NS)
	Pooled	9.7	10 (NS)
Left-sided colitis	A3921094	12.7	8 (NS)
	A3921095	19.3	5
	Pooled	16.1	6
Extensive colitis/pancolitis	A3921094	19.6	5
	A3921095	15.8	6
	Pooled	17.9	6

NS = Not significant

Therefore, the evidence provided in this application does not support the use of oral, that is systemic, treatment with tofacitinib 10 mg BID to treat patients who present with signs and symptoms consistent with predominantly proctosigmoiditis. This is consistent with the Adopted Guideline;[2] which states:

> 'The extent and severity of the disease will also influence the choice of mode of administration to be used for example, rectal in proctitis, oral for extensive UC and IV for acute severe colitis'.

Hence, patients with predominantly proctosigmoiditis are most likely to benefit from topical treatment, such as rectal enemas, unless local treatment forms have failed previously. The latter was not specifically stated in the inclusion or exclusion criteria for either induction study.

Since the sponsor did not provide detailed explanation and analysis why its recruited subjects with predominantly proctosigmoiditis (and left-sided colitis too) were preferentially treated systemically rather than locally, no further conclusions can be made at this time. However, if subjects recruited into either induction study had actually been responsive to prior local treatments this could, in part, explain the relative lack of treatment effect in subjects with proctosigmoiditis, and left-sided colitis to a lesser extent. The overall effect of recruiting 'locally responsive subjects' with proctosigmoiditis and left-sided colitis, in the induction studies, would be to reduce the treatment effect of tofacitinib in those mostly likely to benefit that is, those with most extensive disease.

For subjects with left-sided colitis, in Study A3921094, subjects who received tofacitinib 10 mg BID treatment for 8 weeks did not demonstrate statistical separation from placebo for both remission and mucosal healing. However, the corresponding results from Study A3921095, and the pooled analyses, lend support to a clinically meaningful effect for both endpoints.

The results for remission and mucosal healing were generally consistent for those subjects with baseline extensive colitis/pancolitis. This group of subjects are most likely to benefit from 8 weeks tofacitinib 10 mg BID induction treatment.

Severity of disease

There appears to be no universally adopted or validated diagnostic tool or approach in the classification of UC disease severity or what range of total Mayo scores correspond to a particular disease category. The sponsor chose three sub-categories to represent moderate to severe UC disease, which is generally accepted as baseline total Mayo score 6 to 12 (with 12 as the maximum value possible that is, the most severe form of UC disease). The sub-categories used by the sponsor were < 8, 8 to 10 and > 10, but did not provide a non-numerical definition for what each sub-category represented. For the purpose of this evaluation, the evaluator has considered a value < 8 as moderate UC disease, a value between 8 to 10 as severe UC disease and a value > 10 as extremely severe UC disease. These descriptors are meant only to delineate between severity groups for ease of comparison for the data provided in this application.

There was an apparent inverse relationship between treatment effect with increasing disease severity, in both remission and mucosal healing, across the induction studies, and pooled analyses (Table 14). Hence, those subjects who most benefited from 8 weeks of tofacitinib 10 mg BID treatment were subjects with more 'moderate' disease (that is, baseline total Mayo score < 8).

The benefit of tofacitinib 10 mg BID treatment for subjects with 'severe' UC disease (baseline total Mayo score 8 to 10) is less clear, with no statistical separation or clinically meaningful results observed in Study A3921094. While the corresponding results from Study A3921095, and the pooled analysis, demonstrated statistical separation versus placebo treatment for subjects with baseline total Mayo score 8 to 10, the clinical meaningfulness of having to treat 11 subjects for 8 weeks with tofacitinib 10 mg BID treatment to achieve one case of remission in this sub-population is limited.

For those subjects with 'extremely severe' UC disease (that is, baseline total Mayo score > 10), while the remission results demonstrated statistical separation between subjects who received tofacitinib 10 mg BID treatment versus those who received placebo treatment, the clinical meaningfulness of having to treat 13 subjects for 8 weeks with tofacitinib 10 mg BID treatment to achieve one case of remission in this sub-population is very limited. Furthermore, the total number of subjects from the pooled analysis with baseline 'extremely severe' UC that demonstrated remission at Week 8 was just 11 subjects. In addition, given tofacitinib 10 mg BID treatment did not demonstrate either statistical separation from placebo treatment or a clinically meaningful benefit in the 'extremely severe' UC population for mucosal healing, the risk-benefit balance for this group of patients becomes negative.

Table 14: Remission and mucosal healing at Week 8 in induction Studies A3921094 and A3921095 and pooled results by baseline severity of disease, treatment difference from placebo and number needed to treat (full analysis set, non-responder imputation, central read)

Endpoint Subgroup	Induction Study	Treatment difference from placebo	Number need to treat
Remission			
Total Mayo score < 8	A3921094	26	4
	A3921095	25.9	4
	Pooled	26.1	4
Total Mayo score 8 to 10	A3921094	6.5	15 (NS)
	A3921095	11.6	9
	Pooled	8.9	11
Total Mayo score > 10	A3921094	8.7	11
	A3921095	6.8	15
	Pooled	7.7	13
Mucosal Healing			
Total Mayo score < 8	A3921094	27.3	4
	A3921095	30.6	3
	Pooled	29.2	3
Total Mayo score 8 to 10	A3921094	13.2	8
	A3921095	16.9	6
	Pooled	15	7
Total Mayo score > 10	A3921094	11.6	9
	A3921095	4.5	22 (NS)
	Pooled	8.5	12 (NS)

NS = Not significant

Summary of evaluation of response

The results for remission and mucosal healing were generally consistent with those subjects with baseline total Mayo score < 8 that is, more moderate UC disease, most likely to benefit from 8 weeks tofacitinib 10 mg BID induction treatment.

The evidence provided in this application for treatment benefit in subjects with 'severe' UC disease (baseline total Mayo score 8 to 10) is less convincing, with conflicting results for remission at Week 8 between the induction studies and a relatively high NNT (11) to achieve one case of clinical remission. Of concern is that this baseline disease category group comprised almost 70% of the pooled study population of 905 subjects. Based on subject NNT analysis comparisons, approximately three times as many subjects with baseline total Mayo score 8 to 10 will be needed to be treated with tofacitinib 10 mg BID than subjects with baseline total Mayo score < 8, to achieve one case of remission that is, pooled NNT 4 versus pooled NNT 11, respectively.

The results from the individual induction studies and the pooled analyses for both remission and mucosal healing do not provide compelling evidence to support tofacitinib 10 mg BID induction treatment for 8 weeks in those subjects with the most severe UC disease (that is, baseline total Mayo score > 10).

According to the Adopted Guideline:

> 'Disease severity can be classified into 3 main categories, mild, moderate and severe UC. As disease severity is a very important factor in determining standard treatment inclusion of patients into Phase III trials should preferably be limited to only one of these categories. Alternatively 2 categories may be included (for example, mild to moderate) but in that case the study should allow for separate estimation of effect size in both groups.'[2]

The sponsor aimed to demonstrate a clinical benefit from tofacitinib 10 mg BID treatment in both moderate and severe categories of UC disease. However, the sponsor combined these categories within each of its pivotal Phase III induction studies (Studies A3921094 and A3921095). Furthermore, no separate estimation of effect size appeared to be included in each Study Protocol or Statistical Analysis Plan. The baseline total Mayo score in each induction study was provided as a mean and median value in the clinical study report, not by a breakdown into disease severity (moderate, severe or numerical values to reflect severity). Furthermore, the primary and secondary efficacy analyses from each induction study, and most pooled results, did not allow for separate estimation of treatment effect according to severity of disease.

Provision of results for disease severity, using aggregated or pooled analyses, upon which a decision to register a product is based, is unacceptable and significantly deviates from the adopted guideline[2] advice. This approach has the potential to skew the results in favour of an overall treatment effect, while potentially masking inadequate treatment effects for specific population sub-groups. This has been borne out within this clinical question, as a clear relationship between treatment effect and disease severity has been demonstrated. The sponsor provided no justification or explanation in its submission dossier for its decision to deviate from the adopted guideline.[2]

Notwithstanding the fact there is no universally agreed definition or measurement of moderate to severe UC, and the induction studies were not designed to provide separate size estimation based on disease severity, the evidence provided in this application suggests the benefit-risk balance for those with the most severe UC disease (baseline total Mayo score > 10) is negative. Furthermore, subjects with baseline total Mayo score 8 to 10 have a borderline benefit at best.

Question 4

How do the baseline demographic and disease characteristics compare between subjects who responded to tofacitinib 10 mg treatment in the pivotal Phase III induction studies (Studies A3921094 and A3921095), against those subjects who were classified as 'non-responders' to tofacitinib 10 mg treatment in the same studies?

Sponsor's response

The sponsor provided a succinct table that listed baseline demographic and disease characteristics for Week 8 clinical responders and clinical non-responders in each of the pivotal induction studies (Studies A3921094 and A3921095), as well as a pooled results comparison from the induction studies for clinical responders and non-responders.

Evaluation of response

The information provided in the sponsor's response is acceptable. Generally, baseline demographics (for example age, sex and race) were similar across the inductionstudies (Studies A3921094 and A3921095) in subjects receiving tofacitinib 10 mg BID treatment, irrespective of clinical response status at Week 8.

Baseline disease characteristics between responders and non-responders were generally similar across induction studies for mean duration of UC, extent of disease* and total Mayo score in the < 8 and 8 to 10 subcategories. However, there were a larger proportion of subjects in the pooled non-responder group compared with pooled clinical responders, with higher baseline:

1. Disease severity (that is, baseline total Mayo score > 10; 22.3% versus 10.9%),
2. Prior TNFi exposure (60.9% versus 48.8%, respectively); and
3. Prior TNFi failure (59.4% versus 45.5%, respectively)

*As expected from clinical Question 3, there were proportionately more non-responders to tofacitinib 10 mg BID treatment than responders at Week 8 induction (across studies and pooled results) with proctosigmoiditis (pooled analysis: 16.4% versus 13.3%, respectively) and left-sided colitis (pooled analysis: 36.0% versus 32.5%, respectively) and proportionately less non-responders with more extensive disease (pooled analysis: 47.5% versus 54.0%, respectively).

Consistent with the results identified in clinical question 3, proportionately fewer subjects with the most severe UC disease benefited from 8 weeks induction treatment with tofacitinib 10 mg BID compared with subjects with less severe disease. This is also demonstrated in Table 15, which shows a reduction in clinical response by baseline total Mayo score with increasing disease severity for responders, with a corresponding increase in the proportion of non-responders with worsening disease severity.

Table 15: Proportion of subjects by total Mayo score by induction Week 8 clinical response among subjects who received tofacitinib 10 mg BID in induction Studies A3921094 and A3921095 (full analysis set, non-responder imputation, central read)

Induction treatment, n (%)	Proportion of subjects by total Mayo score, n (%)			
	< 8	8 to 10	> 10	Total
Tofacitinib 10 mg BID				
Week 8 responder	97 (67.8)	367 (59.4)	57 (40.1)	**521**
Week 8 non-responder	46 (32.2)	251 (40.6)	85 (59.9)	**382**
Sub-total	143 (15.8)	618 (68.4)	142 (15.8)	**903**
Placebo BID (n only)	40	152	41	**233**
Total	**183**	**770**	**183**	**1136**

Source: Table 1 S31 Request (S4) & Figure 3 p56 CER

Safety

Question 5

What are the blood results (absolute lymphocyte and absolute neutrophil counts) for Subject [information redacted], who died from acute myeloid leukaemia in Study A3921139, for the period 10 November 2014 to 1 December 2015, by study visit?

Sponsor's response

As requested, the sponsor provided additional tabulated absolute lymphocyte and absolute neutrophil count data for Subject [information redacted], who died from AML while participating in Study A3921139 on tofacitinib 10 mg BID, having completed the induction Study A3921095 (received tofacitinib 10 mg BID) and completed four months of placebo treatment in the maintenance Study A3921096. The subject had treatment-related AEs of moderate neutropaenia and moderate leukopaenia.

Evaluation of response

From the tabulated results provided by the sponsor:

- There were moderate reductions in absolute lymphocyte count within a few months of exposure to tofacitinib 10 mg BID treatment in both the induction Study A3921095 and the open label extension Study A3921139, with subsequent gradual return to the subject's baseline value after cessation of induction treatment, and a normalisation of lymphocyte count after 3 months open label tofacitinib treatment. These results are consistent with the known pharmacology of tofacitinib.

- Apart from a single lymphocyte result on Day 30 of open label treatment, every lymphocyte count result provided was below the reference range, but within the < 0.50 x 10^3/μL cut-off. Hence, Subject [information redacted] satisfied the entry criteria, even though they had mild/borderline leukopaenia at study entry, and at most time points thereafter.
- During the subject's participation in the induction and maintenance studies, and until Day 267 of the open label extension study, the neutrophil counts at all time points remained above the reference range of 2.03 to 8.36 x 10^3/μL.
- From Days 267 to 273, Subject [information redacted] developed moderate severity leukopaenia and neutropaenia.

The sponsor's response is generally acceptable. Given the subject's case was also reviewed by the Malignancy Adjudication Committee, and a determination was made that there was no relationship between the subject's exposure to tofacitinib and the adverse events (moderate leukopaenia and moderate neutropaenia) that preceded a diagnosis of AML that lead to the subject's death, the investigator's assessment that considered there was no linkage between the subject's tofacitinib exposure and the adverse effects is supported on this occasion.

However, it is noted that the Summary of Safety Concerns in the draft Risk Management Plan (RMP, Version 2, dated 20 June 2017: data lock point 16 December 2016), continues to list malignancy (excluding non-melanoma skin cancer) as an Important Potential Risk. This by definition includes AML, and so an association with tofacitinib exposure with AML cannot be ruled out until longer term safety data becomes available.

PI and CMI

Question 6

How do the Baseline demographic and disease characteristics compare between subjects who responded to tofacitinib 10 mg treatment in the pivotal Phase III induction studies (Studies A3921094 and A3921095), against those subjects who were classified as 'non-responders' to tofacitinib 10 mg treatment in the same studies, entered the open label extension study (Study A3921139) and achieved a meaningful clinical response after an additional 2 months of tofacitinib 10 mg treatment?

Sponsor's response

The sponsor provided a succinct table that provided comparative pooled data of baseline demographic and disease characteristics for Week 8 clinical responders from the pivotal induction studies (Studies A3921094 and A3921095) who had received tofacitinib 10 mg BID treatment against clinical non-responders from the induction studies who entered the open label extension study (Study A3921139) as the 'IndNR' (induction non-responder) subpopulation (n = 295) and who achieved a clinical response at the Month 2 assessment with a further 2 month's treatment with open label tofacitinib 10 mg BID (n = 148).

The sponsor also included a response to comments on the draft PI (clinical aspects), which included efficacy and safety data and detailed discussion to support the sponsor's claim for an extended 16 week induction regimen, however discussion of this is beyond the scope of the AusPAR.

Evaluation of response

Approximately 50% of non-responders at the end of their induction treatment went on to achieve a clinical response after a further 2 months of open label tofacitinib 10 mg BID treatment.

The differences in baseline demographic and disease characteristics between the induction Week 8 clinical responders to tofacitinib 10 mg BID treatment and those induction non-responders who achieved clinical response after a further 2 months open label tofacitinib 10 mg BID treatment (IndNR responders) are essentially the same as those described under clinical question 4 response.

- Generally, baseline demographics (for example age, sex and race) were similar between the induction Week 8 clinical responders and the open label 2 month IndNR responders;
- Disease characteristics between induction Week 8 clinical responders and the open label 2 month IndNR responders were generally similar for mean duration of UC, extent of disease (with less extensive colitis/pancolitis and more proctosigmoiditis and left-sided colitis, in the IndNR responders) and total Mayo score categories < 8 and 8 to 10.

However, there were a larger proportion of subjects in the pooled IndNR responder group compared with pooled Week 8 clinical responders, with higher baseline:

1. Disease severity (that is, baseline total Mayo score > 10; 20.3% versus 10.9%, respectively),
2. Prior TNFi exposure (59.5% versus 48.8%, respectively); and
3. Prior TNFi failure (57.4% versus 45.5%, respectively).

These results suggest patients most likely to benefit from treatment have a) less severe UC disease, b) less prior exposure to TNFi treatment and c) less prior failure to TNFi treatment. Furthermore, these results might also suggest that prolonged exposure to tofacitinib 10 mg BID treatment, beyond 8 weeks initial treatment may benefit some persons who did not achieve an adequate clinical response at 8 weeks that is, some persons with more difficult to treat or severe UC disease may benefit from an extended induction. This forms the basis of the sponsor's claim for an extended induction to 16 weeks.

Overall summary of evaluation of sponsor's response to clinical questions

Generally the sponsor's responses, including supporting data, were acceptable and relevant to the clinical questions.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of tofacitinib citrate in the proposed usage are outlined in Table 16.

Table 16: Second round assessment of benefits

Benefits	Strengths and Uncertainties
A tofacitinib 10 mg BID regimen produces a clinically meaningful treatment response (remission and mucosal healing) in an 8 week induction regimen in patients with moderately active ulcerative colitis. A clinically meaningful response was noted as early as 2 weeks post-Baseline and persisted throughout the study duration.	The lowest effective dose that may induce remission in the target population remains unknown. The sponsor provided post hoc analyses using sparse pharmacokinetic data from the Phase II dose-ranging induction study (and post hoc analyses using sparse PK data from the Phase III pivotal induction studies) to support a 10 mg BID dose regimen. Such analyses need to have a high degree of precision and reproducibility, and have potential to introduce bias into the study design, which may affect the validity of the study results. No analysis of the minimum effective dose was calculated or discussed in any model. The baseline demographic and disease characteristics of the induction non-responders has been presented in clinical Question 4. Non-responders generally had less extensive colitis, more severe UC disease and more refractory treatment to prior TNFi exposure or TNFi failure.
Patients with more extensive/pancolitis UC disease appeared to derive the greatest therapeutic benefit from induction treatment	This category of UC disease generally represents the majority of cases.
Patients with left-sided colitis generally benefitted from induction treatment	Non-responders to 8 weeks induction treatment with tofacitinib generally had more left-sided colitis than clinical responders. It is unknown what proportion of subjects who entered the Phase III studies had prior failure of topical treatments, as this was not a requirement for study participation.
As a first in class new chemical entity tofacitinib offers an alternative to other second-line treatments	A proportion of patients who have not tolerated or responded to other treatments may benefit from treatment

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of tofacitinib citrate in the proposed usage are outlined in Table 17.

Table 17: Second round assessment of risks

Risks	Strengths and Uncertainties
Patients with proctosigmoiditis did not benefit from induction treatment with tofacitinib 10 mg BID	It is unknown what proportion of subjects who entered the Phase III studies had prior failure of topical treatments, as this was not a requirement for study participation.
Patients with the most severe baseline UC disease (total Mayo score greater than 10) are highly unlikely to benefit from 8 weeks induction treatment (and even those treated for up to 16 weeks with tofacitinib 10 mg twice a day treatment).	This would also provide support not to extend the induction regimen to 16 weeks as the sponsor has proposed, since a reasonable proportion of the non-responder population at Week 8 induction fall within the same Baseline UC disease category.
Patients with less severe Baseline UC disease (total Mayo score greater than 8 and less than 10) are highly unlikely to benefit from 8 weeks induction treatment. Approximately three times as many patients will need to be treated with tofacitinib 10 mg BID for 8 weeks to achieve one case of remission than patients with more moderate disease.	While the benefit for this category has borderline efficacy, approval in this subpopulation will result in a negative benefit-risk balance as, in all probability, these patients, particularly the more severe and refractory cases will not only be exposed to a further 8 week's high-dose tofacitinib induction treatment but will most likely need to be maintained on a 10 mg tofacitinib BID regimen long-term, in which the adverse effects from tofacitinib treatment will be expected to be considerably higher than those treated with a 5 mg BID dose regimen, especially in terms of AEs of special interest such as serious infections, HZ infections, opportunistic infections (for example TB) and some malignancies Exclusion of this category would also provide support not to extend the induction regimen to 16 weeks as proposed.
Extension of induction exposure from 8 weeks to 16 weeks noticeably increased the incidence of AEs of special interest for example serious infections	Exposure of 16 weeks tofacitinib 10 mg BID treatment, often in the most severe UC disease and refractory cases may give rise to some clinical improvement in some patients. However, given the lack of intermediate assessment periods in the 8 to 16 week extension period, no placebo control to adjust for underlying natural disease progression, the lack of determination of treatment effect in each disease category and location of disease, if there is an optimum period between 8 to 16 weeks for induction then it cannot be determined from the additional data from the open label extension study. Persons who did not respond to treatment over 16 weeks may have unnecessarily been exposed to possibly 6 to 7 more weeks' high-dose tofacitinib for no clinical gain. This is unacceptable. Removal of the severe UC disease indication allows for removal of the extended period for

Risks	Strengths and Uncertainties
	induction and thereby takes a more responsible safer approach to management of the target population and subject persons to unnecessary risk when the likely clinical benefit will be small.
Since the sponsor did not analyse efficacy data in relation to severity of disease and did not use a tofacitinib induction dose below 10 mg BID, this could have the potential to expose those with more moderate disease to unacceptably higher risk than necessary, since the lowest effective dose should be used.	The mathematical models used to assess optimal induction dosing did not provide breakdown by disease severity hence the optimum doses used for each severity category remains unknown. Notwithstanding the unknown minimum effective induction dose, the risks of 8 weeks tofacitinib 10 mg BID treatment appear to be outweighed against the benefit derived for the more moderately disease subpopulation.
Development program for UC: planning and conduct and multiple deviations from the adopted guideline.[2] Bias and confounding may have been introduced into each Phase of the UC development program by the use of retrospective analyses and major protocol amendments that required sample size calculations and affected randomisation schedules. Each issue in turn was addressed throughout the clinical evaluation process but taken as a whole the UC development program should have been more carefully planned so as not to compromise the integrity of the studies and the validity of the results, both internally and externally.	If the adopted guideline had been more closely followed, or the TGA consulted prior to submission or at least justification for every guideline deviation provided then many of the issues raised in this evaluation could have been addressed or negated.

Second round assessment of benefit-risk balance

The benefit-risk balance of Xeljanz (tofacitinib citrate) is unfavourable given the proposed usage, but would become favourable if the recommended changes are adopted.

Induction

The results for remission and mucosal healing were generally consistent for those subjects with baseline total Mayo score < 8 that is, more moderate UC disease. This patient subgroup is most likely to benefit from 8 weeks tofacitinib 10 mg BID induction treatment (NNT 4 and 3, respectively for remission and mucosal healing). However, the evidence provided in this application for treatment benefit in subjects with 'severe' UC disease (baseline total Mayo score 8 to 10) is less convincing, with conflicting results for remission at Week 8 between the induction studies and a relatively high NNT (11) to achieve one case of clinical remission. Based on subject NNT analysis comparisons, approximately three times as many subjects with baseline total Mayo score 8 to 10 will be needed to be treated with tofacitinib 10 mg BID than subjects with baseline total Mayo score < 8, to achieve one case of remission that is, pooled NNT 4 versus pooled NNT 11, respectively. In contrast, the results from the individual induction studies and the pooled analyses for both remission and mucosal healing do not provide compelling evidence to support tofacitinib

10 mg BID induction treatment for 8 weeks in those subjects with the most severe UC disease (that is, baseline total Mayo score > 10) that is, pooled NNT 13 for remission and 12 for mucosal healing (not statistically significant).

Approval for tofacitinib 10 mg induction treatment for more severe forms of UC disease, will, in all probability result in an inadequate response at 8 weeks in a sizeable proportion of patients, who will, should the sponsor's proposed dosing recommendations be accepted, require a further 8 week's high dose tofacitinib BID treatment. Again, given those patients identified as refractory include more severe UC categories, the 10 mg BID regimen will continue into maintenance treatment for those who respond to treatment, potentially for long periods of time and with this a concomitant rise in adverse events can be expected, especially in terms of AEs of special interest such as serious infections, HZ infections, opportunistic infections (for example tuberculosis) and some malignancies.

The sponsor deviated from the adopted guideline[2] on multiple occasions without comment or justification, except for one occasion, namely the recruitment of subjects into the maintenance study who had a clinical response after induction treatment rather than those who had had remission. The more robust/stringent measure is to determine the effect of treatment on sustaining remission. The risk of allowing a high proportion of responders rather than remitters into the maintenance study, while adequately justified in this instance by the sponsor, may lead to a false impression that tofacitinib is more beneficial for the intended population than it may actually be.

Given the identified risks with tofacitinib exposure and the past concerns for safety identified by the TGA and other international regulatory jurisdictions, the evaluator considers the recommendation to restrict treatment to moderate UC patients (baseline total Mayo score < 8) is justified given the borderline efficacy results of the 8 to 10 category and the potential exposure this group may receive for little, if any, clinical benefit against the much higher risk of high dose tofacitinib treatment (for induction and maintenance) than those with more moderate UC disease, especially the risk of increased incidence of adverse events of special interest.

Maintenance

Efficacy was demonstrated for both the 5 mg and 10 mg BID dose regimens in a dose dependent manner. However, the treatment differences between the two dose regimens were not generally clinical meaningful. Given there was also a general dose dependent trend for adverse events, especially for adverse events of special interest (such as serious infections, HZ reactivation and some malignancies), the sponsor has proposed a routine maintenance regimen of 5mg twice a day and this is supported on both efficacy and safety grounds.

Uncertainties

Notwithstanding that the minimum effective induction dose was not adequately described or determined, it is possible that some patient groups such as patients with more moderate UC disease at induction Baseline would still achieve remission with a lesser dose than 10 mg BID but this remains unknown. If the 'optimum' dose regimen was lower than 10 mg for some patient subgroups this would mean an expected reduction in adverse events and hence more favourable benefit-risk balance in such groups.

Furthermore, for the proposed extended induction period to 16 weeks, the actual optimum time to cease induction treatment, and who is most likely to benefit from an extended induction period, has not been determined. An indication restricted to the more moderate UC disease subpopulation reduces the need for the extended induction period altogether and thereby will considerably reduce overall risk and uncertainty in an unwell population, who are resistant to treatments and may potentially be given tofacitinib for protracted periods when the risk of adverse events may clearly outweigh any treatment

benefit, especially since patients and their clinicians might interpret the dosing period as supported by robust Phase III induction studies, when in fact it is not.

Overall comment

Given tofacitinib is a first in class active substance for the treatment of UC disease, in which other UC treatments have failed, or the patient has not tolerated, the availability of another second-line treatment option, particularly for those with more moderate UC disease is supported in this application.

Second round recommendation regarding authorisation

Approval of tofacitinib citrate is recommended:

> *…for the induction and maintenance of treatment of adult patients with moderate active ulcerative colitis, who have had an inadequate response, lost response, or were intolerant to conventional therapy*.

Other recommended conditions are:

- Induction treatment for tofacitinib 10 mg BID period should be limited to 8 weeks only; and
- Patients with proctosigmoiditis should not receive tofacitinib induction treatment unless there is documented prior failure from topical treatment(s).

VI. Pharmacovigilance findings

Risk management plan

Summary of RMP evaluation[6]

- Xeljanz is currently approved for the treatment of moderate to severe active RA in adults who have had an inadequate response or are intolerant to MTX.
- At the time this application was under evaluation, an application was currently under evaluation by the TGA for tofacitinib to extend the indications to include the treatment of active PsA in adult patients (submission PM-2017-03802-1-3).
- The dosage for patients with ulcerative colitis is initially 10 mg BID reducing to 5 mg BID for maintenance treatment. The recommended dose of tofacitinib for RA and PsA is 5 mg BID.
- In support of the extended indications (ulcerative colitis), the sponsor has submitted EU-RMP version 2.0 (dated 20 June 2017; data lock point 16 December 2016) and Australian Specific Annex (ASA) version 1.0 (dated 1 December 2017).

[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 labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- The most recently evaluated EU-RMP was version 3.0 (dated 26 July 2017; data lock point 7 March 2017) and ASA version 1.0 (date 27 September 2017).
- The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 18.

Table 18: 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[1,2,6,7]	ü	ü[4,5]
	HZ reactivation	ü	ü[1,2,7]	ü	ü[4,5]
	Decrease in neutrophil counts and neutropenia	ü	–	ü	ü[4]
	Decrease in lymphocyte counts and lymphopenia	ü	ü[1]	ü	ü[4]
	Decrease in haemoglobin levels and anaemia	ü	–	ü	ü[4]
	Lipid elevations and hyperlipidaemia	ü	–	ü	ü[4]
	NMSC	ü	ü[1,2,6]	ü	ü[4,5]
	Transaminase elevation and potential for drug-induced liver injury	ü	ü[1,6]	ü	ü[4,5]
	Hypertension	ü	–	ü	–
	Creatine kinase increase	ü	–	ü	–
	Weight increase	ü	–	ü	–
Important potential risks	Malignancy (excluding NMSC, including lymphoma: wording in the ASA)	ü	ü[1,2,6,7]	ü	ü[4]
	Cardiovascular risk	ü	ü[1,2,7]	ü	–
	Gastrointestinal perforation (Important Identified Risk in the ASA)	ü	ü[1,2,6,7]	ü	ü[4,5]
	Interstitial lung disease	ü	–	ü	ü[4,5]
	Progressive multifocal leukoencephalopathy	ü	ü[1,2]	–	–
	Increased immunosuppression when used in combination with biologic DMARDs and immunosuppressants including B lymphocyte depleting agents (Missing Information in the ASA)	ü	ü[6]	ü	ü[4,5]
	Increased risk of adverse events when tofacitinib is administered in combination with MTX	ü	ü[1,2]	ü	ü[4,5]

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
	Primary viral infection following live vaccination	ü	–	ü	ü[4]
	Increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors	ü	–	ü	ü[4,5]
	Off-label use including children with JIA or IBD	ü	–	ü	–
	Higher incidence and severity of adverse events in the elderly	ü	ü[1,2]	ü	ü[4,5]
	Rhabdomyolysis	ü	–	–	–
	EBV-related events	ü	–	ü	ü[4,5]
	QT prolongation	ü	–	ü	–
	Reduction in renal function	ü	–	ü	ü[4,5]
Missing information	Effects on pregnancy and the foetus	ü	ü[3,6]	ü	ü[4,5]
	Use in breastfeeding	ü	ü[6]	ü	ü[4,5]
	Effect on vaccination efficacy and the use of live/attenuated vaccines	ü	ü[6]	ü	ü[4,5]
	Use in paediatric patients	ü	ü[1]	ü	–
	Use in patients with mild, moderate, or severe hepatic impairment	ü	ü[6]	ü	ü[4]
	Use in patients with 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	–

1) Clinical trial. 2) PASS. 3) Pregnancy registry. 4) Prescriber information Pack. 5) Patient Alert Card. 6) EU based survey for gastroenterologists. 7) Active surveillance study. JIA = juvenile idiopathic arthritis, IBD = inflammatory bowel disease. Green highlighted text shows the safety concerns that are specific to the ASA. Blue highlighted text shows the safety concerns that are currently only specific for the EU-RMP. Round 2 update – the sponsor has agreed to add these safety concerns to the next ASA revision but has not yet provided an updated ASA.

- The sponsor has agreed to update the summary of safety concerns for Australia to include all safety concerns included in the EU-RMP.
- The additional pharmacovigilance activities are acceptable for the proposed extension of indication.

- The proposed range of additional risk minimisation activities is consistent with what has previously been agreed for this product, and remains acceptable. The sponsor has agreed with the RMP evaluator's recommendation to develop stand-alone risk minimisation materials (prescriber's guide, patient guide, medical alert card and health practitioner's guide for non-prescribing healthcare professionals) for the ulcerative colitis indication.

New and outstanding recommendations from second round evaluation

The sponsor has committed to provide the following to the TGA:

- An updated ASA that includes the following additional information or amendments:
  - The safety concerns that are included in the EU-RMP, as specified;
  - Consolidating the various versions of the ASAs into a single ASA to ensure adequate version control and to cover all indications;
  - Submission dates for clinical study reports; and
  - Including additional information regarding the tracking and reporting of distribution of educational materials in the updated ASA.
- Revised educational materials prior to distribution (see Recommendation 8).
- The following separate educational materials to serve as stand-alone risk minimisation activities for UC:
  - Prescriber's Guide
  - Patient Guide
  - Medical Alert Card
  - Healthcare Practitioner's Guide

Recommendation 7

This is an outstanding recommendation from the first round evaluation report. The sponsor should describe the target number/percentage of gastroenterologists that will represent successful distribution of the risk minimisation materials (which should be the vast majority of gastroenterologists likely to treat patients with ulcerative colitis), how it will determine that it has achieved this target, and the timing of mail out(s) to prescribers. The sponsor should explain whether its existing database includes all gastroenterologists, and how it ensures that this list is complete and updated. The sponsor should also describe the health professional groups that are the target audience for the healthcare practitioner guide for non-prescribers, how the guide will be distributed to them, and how the sponsor will determine that it has achieved adequate distribution. The sponsor should also describe how it will determine that it has achieved adequate distribution of the materials for patients. The sponsor need not report to the TGA the number of attendees at educational meetings, as educational meetings are not considered to be part of the risk minimisation plan.

Recommendation 8

This is an outstanding recommendation from the first round evaluation report. The sponsor has committed to providing updated educational material to the TGA prior to distribution. The sponsor should provide the materials to the TGA at least 6 weeks prior to the launch of the new indication and/or the start of the product familiarisation program and patient support program, whichever is earliest.

Recommendation 9

This is an outstanding recommendation from the first round evaluation report. The sponsor commits to providing stand-alone additional risk minimisation activities for UC, and providing these to the TGA prior to distribution. The sponsor should provide this at least 6 weeks prior to the launch of the new indication and/or the start of the product familiarisation program and patient support program, whichever is earliest.

Recommendation 12

The sponsor should provide the updated ASA to the TGA within three months of approval.

Recommendation 13

The FDA has required the sponsor to conduct a long term, observational study to assess the long term safety of tofacitinib 5 mg BID or 10 mg BID versus other therapies used in the treatment of adults with moderately to severely active ulcerative colitis where the primary outcome of the study is malignancy. The sponsor is required by the FDA to submit a protocol for this study to the FDA by September 2018, with the final study report due in June 2026. This study should also be included as an additional pharmacovigilance activity in the ASA. The RMP/ASA revised with interim and final study outcomes should be submitted to the TGA when available.

Proposed wording for conditions of registration

> The Xeljanz EU-Risk Management Plan (RMP) (version 2.0, dated 20 June 2017, data lock point 16 December 2017), with Australian Specific Annex (version 1.0, dated 1 December 2017), included with submission PM-2017-04764-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

The following wording is recommended for the PSUR requirement (two options, depending on whether we are aligning with EU reporting dates):

> An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). (insert option 1 or 2, below).
>
> Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
>
> The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

As the indications for Xeljanz are being extended into a significantly different population and/or disease/condition it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> Xeljanz (tofacitinib) is to be included in the Black Triangle Scheme. The PI and CMI for Xeljanz must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.

VII. Overall conclusion and risk/benefit assessment

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

Background

Background on condition being treated

UC is a chronic, relapsing, inflammatory disease of the colon characterised by alternating episodes of spontaneous remission and relapse. Current treatment options for moderately to severely active UC include: corticosteroids; immunosuppressants such as AZA and 6-MP; TNFi such as infliximab, adalimumab and golimumab; and the anti-integrin treatment, vedolizumab.

Corticosteroids are used during acute flare.

Tofacitinib is a JAK inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of haematopoiesis and immune cell function. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signalling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signalling through the common gamma chain-containing receptors for several cytokines, including IL-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, proliferation and function, and inhibition of their signalling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signalling by additional pro-inflammatory cytokines, such as IL-6 and type I and II interferons. At higher exposures, inhibition of erythropoietin signalling could occur via inhibition of JAK2 signalling.

Australian regulatory status/history

Tofacitinib citrate in 5 mg tablets was first registered in Australia on 13 January 2015 (Submission PM-2012-00788-3-3) for the following indication:

> *Xeljanz is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to 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.*

In the AusPAR summarising that submission the Delegate noted that there was a significant increase in toxicity with increasing dose with more AEs, especially infections, risk of malignancy, gastrointestinal perforations and dyslipidaemia, noted with the 10 mg BID dose level. It is difficult to justify the additional risks seen in the 10 mg BID group in the absence of any proven improvement in inflammatory markers (erythrocyte sedimentation rate (ESR)) or structural benefit.

Prior to this submission the sponsor submitted an application to extend the indications to include active PsA (submission PM-2017-03802-1-3; October 2017).

During the evaluation process for this submission the sponsor submitted:

- One PSUR (January 2018);

- A safety related request and minor editorial changes (submission PM-2018-00945-1); and
- [Information redacted]

Of particular note the safety related request submitted in March 2018 and finalised in April 2018 did not include all the safety related changes made to the US PI in May 2018.

[Information redacted]

Overseas regulatory status

Xeljanz was approved in the USA in 2012. During evaluation of this submission the indications for tofacitinib were extended in the USA to include UC. On 31 May 2018 the CHMP recommended that the indications be extended to include the following:

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

In the USA the indication is:

> *Xeljanz is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).*
>
> *Limitations of Use: Use of Xeljanz in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.*

The UC indication proposed for Australia differs from the above indications. Additionally the following safety restrictions and information were added to the US PI in May 2018:

- The indications were amended to specify a limitation of use such that Xeljanz is not recommended to be given in combination with biological therapies or with potent immunosuppressants such as azathioprine and cyclosporine.
- The Dosage and Administration recommendations were amended to include the following additional limitations to dosing:
  - Do not initiate Xeljanz/Xeljanz XR in patients with an absolute lymphocyte count less than 500 cells/mm^3, an ANC less than 1000 cells/mm^3 or who have haemoglobin levels less than 9 g/dL.
  - Dose interruption is recommended for management of lymphopenia, neutropenia, and anaemia *(see Warnings and Precautions (5.4), Adverse Reactions (6.1))*.
  - Interrupt use of Xeljanz/Xeljanz XR if a patient develops a serious infection until the infection is controlled *(see Warnings and Precautions (5.1))*.
  - Take Xeljanz/Xeljanz XR with or without food *(see Clinical Pharmacology (12.3))*.
  - Swallow Xeljanz XR tablets whole and intact. Do not crush, split, or chew.
- Additional Warnings and Precautions for serious infections, tuberculosis, viral reactivation, gastrointestinal perforations and advice to avoid live vaccinations concurrently with Xeljanz.

Submissions to extend the indications to include moderate to severe ulcerative colitis have also been made in Canada and Switzerland.

Tofacitinib global development programs have been ceased in Crohn's disease, kidney transplantation and more recently in moderate-to-severe chronic plaque psoriasis (2015; negative opinion from the FDA). The removal of the tofacitinib 15 mg treatment arm in the

UC Phase II induction program adds weight to the global uncertainty around tofacitinib and what can be considered an acceptable dose as well as an acceptable level of risk.

Guidance used

The primary guidance document was the EMA Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis.[2]

Quality

There were no chemistry objections to approval of the blister pack presentation of Xeljanz 10 mg tablets. The bottle presentation was not recommended for approval due to an apparent increase in water content over time, such that it was out of specification at the proposed shelf-life limit. The sponsor subsequently agreed to withdraw the bottle presentation.

Nonclinical

There are no objections on nonclinical grounds to the proposed changes to the registration of Xeljanz. The nonclinical evaluator stated that the pharmacology of tofacitinib, based on the literature presented, supports the new indication.

Demonstration of tofacitinib efficacy in ulcerative colitis will rely on the clinical data though it is noted that previous nonclinical data showed anti-inflammatory efficacy in animal models of RA and PsA.

Relative exposure margins in the previously evaluated toxicology studies were high for the 10 mg BID clinical dosing regimen and raise no extra safety concerns.

Clinical

Pharmacology

No new pharmacology studies were included in this submission.

Population PK data (popPK)

A PopPK analysis, based on sparse PK sample data from one Phase II study and three Phase III studies in the clinical development program for UC was consistent with the PK of tofacitinib in a moderate to severe UC population being similar to the PK of tofacitinib from the RA clinical development program, where the 10 mg BID dose was also explored.

Efficacy

A 5 mg BID induction dose regimen was not explored. The doses of tofacitinib studied in the dose finding Study 1063 were 0.5 mg, 3 mg, 10 mg and 15 mg BID. That study did not allow for statistical comparisons between the various doses, however for the primary efficacy measure of clinical response at Week 8, response rates were lower in the 0.5 mg and 3 mg BID dose groups than in the placebo group. Clinical response rates at Week 8 in the placebo, 10 mg BID and 15 mg BID groups were 47.5%, 63.3% and 80% respectively.

There were three pivotal studies, two assessed induction and one assessed maintenance effects of tofacitinib in UC. There was also an open, long term efficacy and safety study. Additional safety information from use of tofacitinib in the management of Crohn's disease and psoriasis (PsO) was included in the dossier.

Induction of remission

Studies A3921094 and A3921095

These studies were of identical design. They were randomised, double blind, placebo controlled, parallel group, multi-centre, multi-national studies to demonstrate superior efficacy of tofacitinib to placebo in inducing remission in subjects with moderately to severely active UC. These studies consisted of a screening period up to 3 weeks, a 9 week double blind treatment period and a 4 week follow up period. The final efficacy evaluation was at Week 8 of the double blind treatment period.

Subjects with moderate to severe UC were randomised 4:1 to receive either tofacitinib 10 mg BID or placebo. Subjects were stratified based on the status of prior treatment with TNFi therapy, corticosteroid use at Baseline, and geographic region. Initially there was a 15 mg BID arm but that was removed from both studies with subsequent recalculations of the randomisation schedule, sample size and power calculations. Subjects assigned tofacitinib 15 mg BID treatment in either study were not included in the analysis sets, but summarised descriptively in separate tables for safety and efficacy. A total of 614 subjects were randomised to Study A3921094 (476 to tofacitinib and 122 to placebo) and 547 (429 to tofacitinib and 122 to placebo) to Study A3921095.

The full inclusion and exclusion criteria are listed in the clinical evaluation report. Of note study subjects were required to have:

- Moderately to severely active UC (total Mayo score of ≥ 6, with a rectal bleeding score of ≥ 1, and an endoscopic sub-score of ≥ 2 on the Mayo score determined within 10 days of Baseline);
- Subjects must have failed or been intolerant (discontinued due to an AE) at least one UC treatment (oral or IV corticosteroids, AZA or 6-MP or TNFi); and
- Stable oral 5-ASA, oral corticosteroids (prednisone equivalent up to 25 mg/day; budesonide up to 9 mg/day) and antibiotics were allowed during the study period.

The Mayo score consists of 4 subscores: stool frequency, rectal bleeding, findings of endoscopy, and physician's global assessment. Each sub-score is rated on a scale from 0 to 3, indicating normal (0) to severe (3) activity with the Mayo score being the sum of the 4 subscores.

The primary efficacy endpoint was the proportion of subjects in remission at Week 8, defined as a total Mayo score of ≤ 2 points, with no individual sub-score exceeding 1 point and a rectal bleeding sub-score of 0.

The key secondary efficacy endpoint was the proportion of subjects with mucosal healing at Week 8 (total Mayo endoscopic sub-score of 0 or 1). Clinical response at Week 8 was a secondary endpoint and was defined as a decrease from Baseline in Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the sub-score for rectal bleeding of at least 1 point or absolute sub-score for rectal bleeding of 0 or 1. The final secondary endpoint was endoscopic remission at Week 8, defined as a Mayo endoscopic sub-score of 0.

The primary analysis was based on the full analysis set with central read of endoscopy. The primary endpoint was compared between treatment groups by the Cochran-Mantel-Haenszel (CMH) Chi-square test, stratified by prior treatment with TNFi therapy (exposure and failure), corticosteroid use at Baseline, and geographic region using Fisher's exact test.

Subjects with missing remission data at Week 8 were treated as non-responders. The non-responder imputation method was used to handle missing values in both the summary presentations and analyses.

Demographic and disease characteristics at Baseline for these studies are shown in the clinical evaluation report. Mean total Mayo score was 9.0. Prior TNFi treatment failure was reported for 51.3% of subjects in Study A3921094 and in 52.1% of subjects in Study A3921095. Concomitant corticosteroids were taken by 45.5% of subjects in Study A3921094 and by 47.7% in Study A3921095. Results for the primary endpoint (remission at Week 8) from both studies are shown in Table 19.

Table 19: Results for the primary endpoint (remission at Week 8)

Study	Tofacitinib, n (%)	Placebo, n (%)	Difference from placebo (95%CI; p)
A3921094	88 (18.5)	10 (8.2)	10.3 (4.3, 16.3; p = 0.007)
A3921095	71 (16.6)	4 (3.6)	13.0 (8.1, 17.9; p = 0.005)

Various sensitivity analyses showed consistent superiority of tofacitinib over placebo for remission at Week 8, as outlined in the clinical evaluation report. Results from TNFi subgroup analyses are shown in Table 20.

Table 20: Results for primary endpoint (remission at Week 8) by TNFi subgroup

Endpoint Category	Subgroup	Placebo, N	10 mg, N	Difference from Placebo and 95% CI (%)[a] △ Tofacitinib 10 mg BID
Remission				
Prior TNFi Exposure	No	104	417	11.2 (3.7, 18.8)
	Yes	130	488	11.8 (8.2, 14.8)
Prior TNFi Failure	No	110	440	12.3 (5.0, 19.5)
	Yes	124	465	10.6 (7.3, 13.9)
Prior TNFi Failure by the Number of TNFi Agents	1	95	312	11.3 (7.0, 15.7)
	≥2	39	153	9.2 (4.8, 13.7)
Prior TNFi Failure by Reason	Primary Non-responder[b]	74	253	6.2 (2.0, 10.3)
	Secondary Non-responder[b]	43	187	16.6 (11.2, 21.9)

Treatment effects for remission at Week 8 (full analysis set, non-responder imputation) were observed across the majority of subgroups in these exploratory analyses with tofacitinib showing similar differences from placebo regardless of previous TNFi experience. Time to onset was assessed in exploratory analyses with efficacy suggested by Week 2.

Superiority of tofacitinib over placebo was also demonstrated for mucosal healing at Week 8 with mucosal healing achieved by about 30% of subjects given tofacitinib and 16% given placebo across the 2 studies. Clinical response at Week 8 was a secondary endpoint. This was achieved by 59.6% tofacitinib versus 32.8% placebo in Study 1094 and by 55.0% tofacitinib versus 28.6% placebo in Study 1095.

Maintenance

Study A3921096

This study was a randomised, double blind, placebo controlled, parallel group, multi-centre, multi-national, maintenance study in subjects with UC who had completed one of the induction Studies A3921094 or A3921095 and had demonstrated clinical response, defined as in the induction studies.

Subjects were re-randomised at Week 0 to receive tofacitinib 10 mg BID, 5 mg BID or placebo in a 1:1:1 ratio to Week 53. They were then eligible for continued open label tofacitinib 5 mg BID or 10 mg BID in Study A3921139. Subjects were to remain on stable doses of their concomitant UC medications during the study treatment period, except for corticosteroids, which were tapered from the Baseline visit.

The primary efficacy endpoint was remission at Week 52. Remission was defined as in the induction studies as a total Mayo score of ≤ 2 points with no individual sub-score exceeding 1 point and a rectal bleeding sub-score of 0. The primary endpoint analysis was based on the centrally-read endoscopic sub-score. A total of 593 subjects were randomised. At Baseline the mean total Mayo score was 3.3, 179 (30.2%) subjects were in remission and 295 (49.7%) had mucosal healing.

The proportion of subjects in remission at Week 52 (full analysis set, non-responder imputation) was statistically significantly ($p < 0.0001$) greater in both the tofacitinib 5 mg BID group (34.3%) and the tofacitinib 10 mg BID group (40.6%) compared with the placebo group (11.1%). The results from sensitivity analyses (generalised linear mixed model (GLMM), responder imputation, responder imputation, multiple imputation and per protocol analysis set (PPAS)) of the full analysis set population, and the modified full analysis set population, were generally consistent with the primary efficacy analysis.

Various subgroup analyses compared remission rates at Week 52 between the two tofacitinib groups and placebo. There were no statistical comparisons between the tofacitinib 5 mg BID and 10 mg BID dose groups. The major differences between study subgroups are listed in the clinical evaluation report. Of note, for the prior TNFi failure subgroup, there was a 12.5% difference in remission rates at Week 52, favouring tofacitinib 10 mg BID compared with 5 mg BID (24.1% versus 36.6%, respectively). This difference was not seen in subjects who did not have prior failure with TNFi treatment. In general, subjects with markers consistent with more severe or more treatment resistant disease at Baseline had higher remission rates with the 10 mg BID dose regimen than with 5 mg BID.

Results for key secondary endpoints are shown the clinical evaluation report. Statistical superiority of each dose regimen of tofacitinib compared with placebo was demonstrated for mucosal healing at Week 52, present in 13.1% of subjects given placebo, 37.4% given tofacitinib 5 mg BID and 45.7% given tofacitinib 10 mg BID. Sustained corticosteroid-free remission at Week 52 among subjects who were in remission at Baseline was achieved by 5.1% of subjects given placebo, 35.4% given tofacitinib 5 mg BID and by 47.3% given tofacitinib 10 mg BID.

The duration of effect after ceasing treatment could be assessed from the placebo group in this study. At Week 8, the first assessment time point, the placebo group had statistically significantly higher adjusted mean high sensitivity C-reactive protein (hsCRP) values compared with both tofacitinib treatment groups. This suggests the effect of tofacitinib is lost quite quickly after cessation of treatment.

Study A3921139

This study is an ongoing, open, long-term extension study in subjects who had completed or demonstrated treatment failure in the maintenance Study A3921096), or who were non-responders after completing one of the induction Studies A3921094 and A3921095. It was primarily a safety study.

Eligible subjects were assigned tofacitinib 5 mg BID or 10 mg BID depending on baseline remission status. Those in remission at Baseline (that is, who were in remission at Week 52 of Study A3921096) received tofacitinib 5 mg treatment while all other subpopulations (including non-responders) received tofacitinib 10 mg treatment. Non-responders who failed to demonstrate clinical response at Month 2 (central endoscopic sub-score read)

were withdrawn from the study. Tofacitinib dose adjustments were permitted after 8 weeks of study treatment. Subjects on baseline corticosteroids needed to continue tapering. There was no primary efficacy endpoint. Secondary efficacy endpoints included remission, clinical remission, mucosal healing and clinical response.

There were 429 induction non-responders with 295 having received 10 mg BID tofacitinib for 8 weeks prior to commencing Study A3921139. Of these 295 non-responders to 8 weeks of tofacitinib 10 mg BID who then continued to receive tofacitinib 10 mg BID in this study, 260 (88%) had an efficacy assessment at Week 8 that is, after a total of 16 weeks treatment with tofacitinib 10 mg BID. Of these, 42 out of 260 (16.2%) were in remission. 265 out of 295 subjects were assessed at Week 8 for mucosal healing and 68 (25.7%) had mucosal healing. 258 out of 295 were assessed for clinical response and 155 (60.1%) had clinical response.

The Delegate notes that the pharmacovigilance plan indicates that a study to evaluate the efficacy and safety of tofacitinib in UC patients in stable remission on 10 mg BID who decrease the dose to 5 mg BID compared to subjects remaining on 10 mg BID for 6 months is planned and is expected to have a final report by the end of 2020.

Safety

Safety risks associated with tofacitinib include serious infection including TB and bacterial, invasive fungal, viral and other opportunistic infections, lymphoma and other malignancies. The major safety issue with this submission is whether the risks associated with the tofacitinib 10 mg BID dose regimen are justified given the extent of efficacy demonstrated by the 10 mg BID dose in induction and maintenance periods in the Phase III studies. In the RA studies an increase in infections, malignancies, gastrointestinal perforations and dyslipidaemia was associated with the 10 mg BID compared with the 5 mg BID tofacitinib dose.

In this submission a total of 938 subjects received 10 mg tofacitinib for 8 weeks in the dose finding and induction studies and a further 282 received 15 mg BID for 8 weeks. In the pivotal maintenance study, 196 subjects received tofacitinib 10 mg BID for up to 52 weeks and a further 914 subjects received a mix of 5 mg and 10 mg BID during the ongoing open maintenance study 1139. Overall the 10 mg BID dose has been received by 506 subjects for at least 12 months in the UC studies.

In the Phase III induction studies there was no consistent difference in the proportion of subjects with AEs across the placebo and 10 mg BID tofacitinib groups, nor in the rate of reporting of serious AEs, severe AEs or discontinuations due to AEs. The most frequent treatment-related AEs in the tofacitinib 10 mg group was headache, in both induction studies: 4.4% and 6.1% for tofacitinib 10 mg in Studies A3921094 and A3921095, respectively versus 3.3% and 5.4% for placebo treated subjects, respectively. There was a higher rate of infections and GI disorders in the tofacitinib groups in both studies.

AEs in the maintenance study 1096 were summarised in the clinical evaluation report and allowed a comparison of events in the 5 mg BID and 10 mg BID tofacitinib dose groups. Slightly higher rates of AEs, SAEs, severe AEs and discontinuations and dose reductions due to AEs were reported with the 10 mg BID dose group compared with the 5 mg BID dose group. Of note, infections and infestations were reported for 24.2% placebo versus 35.9% tofacitinib 5 mg BID versus 39.8% tofacitinib 10 mg BID in that study. Dose related trends were also observed for gastro-oesophageal reflux disease, vomiting, chest pain, cystitis, tooth abscess, bronchitis, folliculitis, gastroenteritis, HZ, oral herpes, urinary tract infection, ALT increased, blood CPK increased, weight increased, back pain, hypercholesterolemia, oropharyngeal pain, dermatitis and dermatitis acneiform. For all these events the total numbers reported and between group differences were quite small. The largest difference was in HZ (1.0% for 5 mg BID versus 5.1% for 10 mg BID).

The Delegate included an Attachment that showed the proportions and incidence rates of AEs of special interest in Cohort 1 (Phase II and III induction studies), Cohort 2 (Phase III maintenance study), the induction non-responder subgroup, and Cohort 3 (Phase II and III long term extension study) in the UC Program (not included in this AusPAR).

Four deaths in the UC program were reported, these were due to: aortic dissection; hepatic angiosarcoma; pulmonary embolism; and AML. Of these events only the angiosarcoma was considered possibly study drug related. The subject with death due to pulmonary embolism was in Study A3921139. That subject developed cholangiocarcinoma and metastases to the peritoneum after having received tofacitinib 10 mg BID for 378 days. This patient died due to pulmonary embolism. Additionally there was 1 event of hepatic angiosarcoma and 1 event of AML reported as the cause of death in 2 tofacitinib-treated subjects in Study A3921139.

There were 10 reports of NMSC all in the maintenance studies (6 in Study A3921139, 1 given tofacitinib 5 mg BID and 5 given tofacitinib 10 mg BID and 4 in Study A3921096, 3 given tofacitinib 10 mg BID and 1 given placebo). The Safety Summary mentioned an additional NMSC case in the maintenance studies. Modelling data from the UC studies predicted incidence rates events out of 100 PY) for placebo, 5 and 10 mg BID tofacitinib using time-weighted average concentrations were: 1.66, 1.84 and 2.06 for serious infections, 0.384, 0.709 and 1.31 for opportunistic infections, 1.32, 2.44 and 4.48 for HZ, and 0.147, 0.342 and 0.796 for NMSC.

In Study A3921139, there were 15 subjects with malignant events: 1 tofacitinib 5 mg and 14 tofacitinib 10 mg. Malignancy, excluding NMSC, was confirmed in 9 subjects, all in the tofacitinib 10 mg BID group. Of the 9 subjects in the tofacitinib 10 mg BID group with confirmed malignancy, excluding NMSC, 3 subjects died during the study: 1 confirmed case each of hepatic angiosarcoma; AML and cholangiocarcinoma.

For the other 6 cases who received tofacitinib 10 mg treatment: 1 case had confirmed (EBV-associated lymphoma considered study drug related; 1 case of moderate cutaneous leiomyosarcoma (study drug related); 1 case of study related moderate essential thrombocythaemia; 1 case of study drug related renal cell carcinoma and 2 cases of non-study drug related malignancies (1 case of severe cervical dysplasia and 1 case of severe adenocarcinoma of colon).

Gastrointestinal perforation was reported in 3 subjects, 1 given placebo and 2 given tofacitinib 10 mg BID. Opportunistic infections were reported in Studies A3921094, A3921095, A3921096 and A3921139. These were most frequently HZ and 1 case each of CMV, histoplasmosis and pulmonary mycosis associated with tofacitinib. Four cases of pulmonary embolism were seen in subjects given the 10 mg BID dose in the extension Study A3921139. Dose dependent increases in HZ infections, serious infections and NMSC were seen.

Risk management plan

The most recently evaluated RMP for this submission was version 3.0 (EU-RMP dated 26 July 2017; data lock point 7 March 2017) and ASA version 1.0 (date 27 September 2017). The sponsor agreed to update the next ASA revision to include additional safety concerns that have been included in the most recent EU-RMP but were not in the submitted ASA. These were: HZ reactivation; increased risk of adverse events when tofacitinib is administered in combination with MTX; primary viral infection following live vaccination; increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors; off-label use including children with JIA or IBD; and higher incidence and severity of adverse events in the elderly.

In addition to updating the ASA the sponsor has committed to provide revised educational materials prior to distribution. These are to include:

- Prescriber's Guide.
- Patient Guide.
- Medical Alert Card.
- Healthcare Practitioner's Guide.

Additionally, with approval of the UC indication, the FDA required the sponsor to conduct a long term, observational study to assess the long-term safety of tofacitinib 5 mg BID or 10mg BID versus other therapies used in the treatment of adults with moderately to severely active ulcerative colitis. That study's primary outcome is malignancy. Secondary outcomes of interest include, but are not limited to, opportunistic infections, thromboembolic events, and hepatic injury. Study subjects are to be followed for at least 7 years. The FDA has noted that the sponsor has advised that a draft protocol for this study is to be submitted in September 2018 and the study to be completed by 2026 with the final study report to be submitted to the FDA in June 2026. Interim and final study reports of that study are to be submitted to the TGA when available.

Recommended conditions of registration

The Xeljanz EU-Risk Management Plan (RMP) (version 2.0, dated 20 June 2017, data lock point 16 December 2017), with ASA (version 1.0, dated 1 December 2017), included with submission PM-2017-04764-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

As the indications for Xeljanz are being extended into a significantly different population and/or disease/condition it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

> Xeljanz (tofacitinib) is to be included in the Black Triangle Scheme. The PI and CMI for Xeljanz must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date the new indication is registered.

Two options were presented by the RMP evaluator for the PSUR reporting requirement, dependent on whether the indication was aligned with the EU reporting dates.

Risk-benefit analysis

Delegate's considerations

Discussion

This submission did not allow for a direct comparative assessment of the benefits and risks of tofacitinib in relation to other treatments for moderate to severe UC. A cross-study comparison with the induction studies for infliximab (described in the infliximab PIs) suggests that the efficacy of tofacitinib 10 mg BID in induction of remission and clinical response may be somewhat less than was demonstrated with infliximab however as with any cross-study comparison there are limitations to the comparison. In this case differences in available patient population are likely to contribute to differences in apparent efficacy due to the lack of prior exposure of any infliximab subjects to a TNFi.

The clinical trial program allowed some assessment of efficacy after 16 weeks of treatment at 10 mg BID for those subjects who did not have a clinical response at Week 8. These subjects were assessed in the ongoing open extension study, 1139 and those results, in my

view, support continuation of treatment for up to 16 weeks at 10 mg BID for those patients who do not have a clinical response at Week 8. The clinical evaluator commented extensively on this issue in the clinical evaluation report. The evaluator does not recommend an induction period of up to 16 weeks primarily because efficacy was based on results from an open, uncontrolled study and AEs are known to be dose related.

The Delegate considers that for some patients, particularly those who haven't adequately responded to other medical treatment and for whom the alternative is surgery, it would be acceptable to allow a further 8 weeks of induction treatment with tofacitinib 10 mg BID. Patients who then fail to adequately respond would be recommended to cease tofacitinib. While the data showing a benefit for these patients was from an open study, efficacy was assessed using the Mayo score, a robust and validated tool for assessment of efficacy of treatments for UC so the open nature of that study is not as significant as it would be for a more subjective measure of efficacy.

The 10 mg BID maintenance dose should only be considered for patients who had an initial clinical response after up to 16 weeks induction treatment and who have subsequently not had an adequate continued response to tofacitinib 5 mg BID. Monitoring for AEs is required for all patients taking tofacitinib and patients moving to a 10 mg BID maintenance dose should be advised that the risks of AEs are increased with that higher dose of tofacitinib.

The claim that a clinical response can be seen from 2 weeks of commencing treatment appears to be based on an exploratory endpoint of change in partial Mayo score over time.

Tofacitinib demonstrated clinically and statistically significant efficacy in subjects who had failed prior TNFi treatment and in TNFi naïve subjects. Although the remission rate was lower in those who had failed TNFi therapy than in TNFi naïve subjects, the difference from placebo was similar for both these subgroups.

The relative safety and efficacy of tofacitinib compared to other available treatments for UC is uncertain however there are considerable safety signals that have recently been detected and that are dose related. A longer term comparative observational safety study is planned. Given these factors it should be considered whether tofacitinib should be restricted in UC to those patients who were either intolerant or unresponsive to other treatments, including biologic agents.

The sponsor initially proposed the UC indication stated:

> *Xeljanz is indicated for the induction and maintenance of treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to conventional therapy.*

In the response to clinical questions, the clinical evaluator had recommended that the PI reflect that tofacitinib should be used only in UC patients with moderate UC (Mayo score < 8 at Baseline) and that it be avoided in patients with principally proctosigmoiditis. These recommendations are based on subgroup analyses from small numbers of patients and the Delegate does not accept those recommendations. The pivotal studies were not designed primarily to assess efficacy in these subgroups, but rather to assess efficacy for moderate to severe UC in total.

The sponsor had proposed to refer to induction and maintenance phases of treatment in the indications. To be consistent with the indications for other systemic UC treatments the indications should refer to UC only. Additionally the Delegate considers that reference to biologic agents should be included in the indications. The indication accepted by the EMA is requested, that is:

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

Summary of issues

- The relative efficacy and safety of tofacitinib compared with TNFi and/or vedolizumab is not clear. A post-market observational study to assess differences in safety outcomes is planned but will not be reported until 2026.
- The RMP evaluator has proposed a black triangle be added to the PI given the increased dose proposed for UC compared with the current RA dose. This is supported by the evaluator and agreed by the sponsor. It is not clear if a boxed warning is also required to highlight the risks from use of tofacitinib. While the US PI has a boxed warning the EU- SPC does not.
- It isn't clear whether tofacitinib should be reserved for UC patients who have inadequate response to or lose response to TNFi or other biologic therapies.

Proposed action

The Delegate has no reason to say, at this time, that the application for Xeljanz (tofacitinib) should not be approved for registration, subject to satisfactory negotiation of the PI and RMP.

Request for ACM advice

1. Please provide comment on the following amended indication proposed by the Delegate:

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

   Does the Committee consider the above proposed indication is appropriate to limit use of tofacitinib in the treatment of UC?
2. Does the Committee consider it appropriate to include a restriction on the use of tofacitinib in the induction Phase of treatment of UC in the indication? Such a restriction would specify a duration within which a clinical response required in order that treatment be continued.
3. The Committee's advice on the extent of warnings regarding dose-related toxicity in the draft PI is requested.

Response from sponsor

Introduction

The sponsor welcomes the opportunity to comment on the issues raised in the Delegate's Summary for consideration by the ACM on the efficacy and safety of tofacitinib 5 mg BID and 10 mg BID in the treatment of moderately to severely active UC in adults. The sponsor supports the indication wording as modified by the Delegate together with the proposed addition of 'either' as follows:

> *Xeljanz is indicated for the ~~induction and maintenance of~~ treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.*

Advice sought

The sponsor acknowledges the Summary of Issues and the Delegate's Request for ACM advice.

1. Please provide comment on the following amended indication proposed by the Delegate:

Xeljanz is indicated for the ~~induction and maintenance of~~ treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to conventional therapy or a biological therapy.

Does the Committee consider the above proposed indication is appropriate to limit use of tofacitinib in the treatment of UC?

As requested by the Delegate the sponsor agrees to remove 'induction and maintenance' and to include 'or a biological therapy' in the proposed indication, and seeks to clarify the treatment further by stating tofacitinib can be used following 'either conventional therapy or a biological therapy'.

In view of the existing unmet medical need across a range of patients with moderately to severely active UC, and the robust clinical data in support of tofacitinib's safety and efficacy in patients who have failed immunosuppressants or corticosteroids (TNFi-naïve) and those who have failed TNFi agents (TNFi failures), the sponsor believes that tofacitinib provides significant benefit as an oral therapy to UC patients who have failed or were intolerant to either of these groups of existing treatment options. This was also recognised by the EMA CHMP's determination that tofacitinib brings significant clinical benefit to patients with UC in comparison with existing therapies, based on a major contribution to patient care. As a result of this assessment and in line with the provisions of Article 14(11) of Regulation (EC) No 726/2004, tofacitinib has been granted an additional year of marketing protection in the EU across all indications.[7]

Tofacitinib is the first oral advanced therapy in many years that provides an effective treatment alternative to existing therapies for both TNFi-naïve and TNFi-failure patients. It exhibits all of the following attributes including:

- Robust induction and maintenance efficacy in patients with prior failure of conventional therapy, including immunosuppressants and corticosteroids.
- Robust and similar induction efficacy in both TNFi naïve and TNFi failures.
- Robust maintenance efficacy in both TNFi naïve and TNFi failures and achievement of corticosteroid free remission.
- Early onset of action.
- Predictable and durable plasma drug exposure without immunogenicity and the burden of need for therapeutic drug monitoring for treatment optimization
- No need for concomitant immunosuppressant therapy
- Overall acceptable safety profile generally similar to TNFi agents with the exception of the manageable risk of HZ.
- Good adherence to a convenient oral therapy due to its low pill burden and good tolerability that can otherwise be challenging in chronic treatment.[8] [9] [10]

In relation to the Delegate's question to the ACM on the proposed indication, the sponsor discusses below the tofacitinib data in these subgroups, followed by a brief discussion on

[7] Xeljanz-h-c-4214-x-0005 European Public Assessment Report, Appendix.
[8] Devine, F. et al. (2018), Barriers to treatment: describing them from a different perspective. *Patient Prefer Adherence*, 2018; 12: 129-133.
[9] Neiman, A. B. et al. (2017), CDC Grand Rounds: Improving Medication Adherence for Chronic Disease Management - Innovations and Opportunities, *MMWR Morb Mortal Wkly Rep*, 2017; 66:1248-1251.
[10] Testa, A. et al. (2017), Adherence in ulcerative colitis: an overview, *Patient Prefer Adherence,* 2017; 11: 297-303.

the relative efficacy and safety as compared to other UC treatments. Current data on tofacitinib in moderately to severely active UC patients demonstrate the following:

- Efficacy for induction was consistent across TNFi-naïve subjects (that is, those who had failed only conventional therapy) and TNFi-exposed/TNF-failures in placebo adjusted remission, mucosal healing and clinical response rates; this was demonstrated in both primary and secondary TNFi-failures.
- In maintenance, patients without prior TNFi-failure showed similar efficacy between tofacitinib 5 mg BID and 10 mg BID; whereas TNFi-failure subjects had a larger gain in efficacy of tofacitinib 10 mg BID over 5 mg BID, which was substantial and clinically meaningful.
- The safety profile of tofacitinib has been well characterized based on a robust safety database in UC as well as an extensive safety database derived from other indications, particularly RA. No new safety signals were identified in the UC program. The safety profile of tofacitinib is generally consistent across indications. The totality of data across indications indicated a dose-relationship for serious infections, HZ and NMSC but a dose relationship was not shown for malignancy (excluding NMSC). In addition, in UC patients, the safety profile was generally similar between tofacitinib (both 5 mg BID and 10 mg BID) and biologics approved for UC, except for a higher rate of HZ with tofacitinib.

Overall, the consistent and clinically meaningful induction and maintenance efficacy in various subgroups based on their treatment experience, together with the manageable safety profile, supports a favourable benefit risk profile in TNFi-naïve and TNF-failure UC patients. These data support the use of tofacitinib as a treatment option for UC patients who have failed conventional therapy as well as patients who have failed TNFi.

Relative Safety and Efficacy

The Delegate states in the Summary of Issues that '…The relative efficacy and safety of tofacitinib compared with TNFi and/or vedolizumab is not clear'. The sponsor notes that while there are no controlled data with direct comparison and there are limitations when interpreting results across studies, tofacitinib data was contextualised with historical data from currently approved treatments, as follows:

- The observed treatment effect of tofacitinib 10 mg BID in induction was at least similar to historical Phase III results of UC treatments approved during the last 10 years including golimumab, vedolizumab, and adalimumab (excluding infliximab for which, as noted by the Delegate, differences in patient population likely contributed to differences in apparent efficacy due to the lack of prior exposure to a TNFi in all subjects in infliximab Phase III trials).
- When analysed by prior TNFi experience, the observed treatment effect of tofacitinib 10 mg BID induction in TNFi-naïve patients was at least similar to the same subgroup of subjects in the comparable development programs; and in patients with prior TNFi exposure or failure, the observed treatment effect of tofacitinib was numerically larger than that for adalimumab and vedolizumab.[11] [12] [13] [14]
- For maintenance therapy, the observed treatment effect of tofacitinib 5 mg BID and 10 mg BID at 1 year for clinical remission was similar to or greater than that for

[11] Feagan, B.G. et al. (2013), Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*, 2013; 369: 699-710.
[12] Vedolizumab FDA AC BD Figure 7-4, accessed from the FDA website 9 November 2018.
[13] Sandborn, W.J. et al. (2012), Adalimumab induces and maintains clinical remission in patients with moderate to severe ulcerative colitis, *Gastroenterology*, 2012; 142: 257-265.
[14] Adalimumab FDA BLA Appendix 4; Appendix 5, accessed from the FDA website 9 November 2018.

historical Phase III results including vedolizumab, golimumab, adalimumab and infliximab.

- When analysed by prior TNFi experience, the observed treatment effect for clinical remission in maintenance for TNFi-naïve patients or patients without prior TNFi failure at either dose of tofacitinib was numerically higher than that for vedolizumab or TNFi (golimumab, adalimumab and infliximab); and in patients with prior TNFi failure, tofacitinib 5 mg BID was numerically lower than vedolizumab but numerically higher than adalimumab, while the results of tofacitinib 10 mg BID were similar to those observed with vedolizumab. [11] [15] [16] [17] [18]
- Based on contextualization using the Truven MarketScan Database, an administrative healthcare claims database in the US, the safety profile of the entire treatment experience with tofacitinib 5 mg BID and 10 mg BID in the UC program was similar to that of TNFi agents, with the exception of a higher IR of HZ or tofacitinib. Similarly, with the exception of higher rates of HZ for tofacitinib, the rates of adverse events of special interest in induction and maintenance were similar to those reported for TNFi agents in published UC induction and maintenance randomised clinical trials.
- Lastly, the sponsor acknowledges that data from the post-marketing observational study ('Corrona') will be available in 2026; however, quarterly updates of unadjusted rates of events of interest will also be reported in the periodic safety update reports submitted to TGA.

Based upon these considerations, the sponsor believes that the data and the rationale provided in the original application and responses, justifies the use of tofacitinib in adult UC patients who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.

2. Does the Committee consider it appropriate to include a restriction on the use of tofacitinib in the induction phase of treatment of UC in the indication? Such a restriction would specify a duration within which a clinical response required in order that treatment be continued.

The sponsor maintains that the most appropriate place to describe limitations on the duration of induction therapy is in PI Section 4.2 Dose and Method of Administration, where there is clear advice that continued treatment is not recommended for patients who have not shown a clinical response by Week 16. The placement of this information would also be consistent with the PI of other treatments approved for use in UC.

The sponsor agrees to most of the Delegate's recommended changes to the PI in the dose and method of administration section including the emphasis on using the lowest maintenance dose, however, the sponsor prefers to retain the statement that continuation of the 10 mg BID dose for maintenance may be most appropriate for refractory patients such as those who have failed prior TNFi therapy. The sponsor believes it is important for prescribers' awareness that individual patients (for example those who have history of failure to multiple agents) may benefit from continuation of the 10 mg BID dose.

3. The Committee's advice on the extent of warnings regarding dose-related toxicity in the draft PI is requested.

[15] Vedolizumab FDA AC BD Figure 7-7, accessed from the FDA website 9 November 2018.
[16] Sandborn, W.J et al. (2014), Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis, *Gastroenterology*, 2014; 146: 96-109.
[17] Adalimumab FDA BLA Appendix 5, accessed from the FDA website 9 November 2018.
[18] Rutgeerts, P. et al. (2005), Infliximab for induction and maintenance therapy for ulcerative colitis, *N Engl J Med*, 2005; 353: 2462-2476.

The totality of data across indications in the broader tofacitinib development program indicated a dose-relationship for serious infections, HZ and NMSC but a dose-relationship was not shown for malignancy (excluding NMSC).

The sponsor agrees to the Delegate's recommended changes to the PI in order to raise awareness of a potentially greater risk of serious infections in patients treated with tofacitinib 10 mg BID, and to indicate that opportunistic HZ infections were observed in patients treated with tofacitinib 10 mg BID.

Regarding malignancies, the sponsor agrees to include the statement that in the long term extension study, malignancies were observed more often in patients treated with tofacitinib 10 mg BID compared with 5 mg BID. However, evaluation of dose dependency was confounded by a marked imbalance in the proportion of subjects treated with 5 mg BID versus 10 mg BID in Cohort 3 (Phase II, Phase III long term extension tofacitinib), which represents the entire treatment experience with tofacitinib in the UC program, with 84% of the subjects categorized to the Predominant Dose 10 mg BID group by design. Overall, malignancies (excluding NMSC) were reported infrequently in the UC program.

The current PI already contains warnings associated with serious infection, HZ virus reactivation, opportunistic infections, NMSC and malignancies (excluding NMSC) such as lymphoma, based on findings in the RA development program. Additionally, the risk that HZ and NMSC may be higher in patients treated with tofacitinib 10 mg BID than in patients treated with 5 mg BID is highlighted. The sponsor also agrees with the RMP evaluator's proposal that a black triangle is added to the PI given the increased dose proposed for UC compared with the currently approved dose for RA.

Lastly, the sponsor notes the Delegate's comments in the Summary of Issues that '…It is not clear if a boxed warning is also required to highlight the risks from use of tofacitinib' since the United States Package Insert (USPI) has a boxed warning and the EU Summary of Product Characteristics (SmPC) does not. The sponsor believes it is important to clarify the existing boxed warning in the USPI was not updated during the Food and Drug Administration (FDA) review of the UC application.

Typically there are regional differences in the use of boxed warnings and in this case the sponsor maintains that the most appropriate placement of warnings regarding serious infections and malignancies is within the body of the PI. There are no boxed warnings in the current tofacitinib PI based on the RA data. As discussed above, the safety profile of tofacitinib is generally consistent across indications and no new safety signals were observed in the UC program compared with the RA program. Therefore, there are no new safety data emerging from the UC program that would warrant the introduction of a boxed warning for the tofacitinib PI. The placement of warnings within the body of the PI would also be consistent with the Australian PIs of other treatments approved for use in UC.

The sponsor looks forward to the outcome of the ACM discussions on this application.

Advisory Committee Considerations[19]

The Advisory Committee on Medicines (ACM) taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Xeljanz film coated tablet containing 10 mg of tofacitinib to have an overall positive benefit-risk profile for the Delegate's amended indication;

> *Xeljanz is indicated for the induction and maintenance of treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to conventional therapy or a biologic therapy.*

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/ Consumer Medicine Information (CMI) amendments

The ACM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific Advice

The ACM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

1. ***Please provide comment on the following amended indication (as proposed by the Delegate):***

   > ***Xeljanz is indicated for the induction and maintenance of treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to conventional therapy or a biological therapy.***

The ACM agreed with the Delegate's proposed amendments to the indication to include *'…or a biological therapy'.*

2. ***Does the Committee consider the above proposed indication is appropriate to limit use of tofacitinib in the treatment of UC?***

The committee considered the above proposed indication to be appropriate to limit the use of tofacitinib in the treatment of UC.

3. ***Does the Committee consider it appropriate to include a restriction on the use of tofacitinib in the induction phase of treatment of UC in the indication? Such a restriction would specify a duration within which a clinical response required in order that treatment be continued.***

The committee did not consider it appropriate to include in the indication a restriction regarding the use of tofacitinib in the induction phase of treatment of UC. Instead the committee recommended placing a restriction on the continuation of ineffective therapy beyond 16 weeks in the 'Dosage and Administration' section of the PI.

[19] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (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.

4. The Committee's advice on the extent of warnings regarding dose-related toxicity in the draft PI is requested.

The committee agreed with the recommendation to add a black triangle to the PI in consideration of the 10 mg higher dose. In addition, the committee also supported the use of a boxed warning to highlight the dose-related toxicity risks associated with the use of the higher strength (10 mg) tofacitinib. The committee agreed that through these warnings, the PI would be able to make clear that there is a higher risk of certain infections (including opportunistic infections such as HZ infections) when treating with a higher dose.

Based on the maintenance therapy data, the 5 mg BID dose was generally as effective as the 10 mg dosing. The committee therefore agreed that a maintenance dose of more than 5 mg BID would be inappropriate due to the dose-dependent risk of serious adverse effects, except in patients who had previously failed maintenance treatment with 5 mg BID. Those patients should have the option of progressing to 10 mg BID for maintenance treatment.

Conclusion

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Xeljanz (tofacitinib as citrate) for new strength 10 mg film coated tablet and existing strength 5 mg film coated tablet for the following new indication:

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

The full indications for the 5 mg tablet are now:

> *Rheumatoid arthritis*
>
> *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 conventional synthetic disease-modifying antirheumatic drugs (DMARDs), including methotrexate.*
>
> *Psoriatic arthritis*
>
> *Xeljanz in combination with conventional synthetic DMARDs is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response to a prior DMARD therapy*
>
> *Ulcerative colitis*
>
> *Xeljanz is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological therapy.*

Specific conditions of registration applying to these goods

- Xeljanz (tofacitinib) is to be included in the Black Triangle Scheme. The PI and CMI for Xeljanz must include the black triangle symbol and mandatory accompanying text for 5 years, which starts from the date the new indication is registered.
- The Xeljanz EU-RMP (version 2.0, dated 20 June 2017, data lock point 16 December 2016), with ASA (version 1.0, dated 1 December 2017), included with submission PM-2017-04764-1-1, to be revised to the satisfaction of the TGA, will be implemented in Australia.

Attachment 1. Product Information

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

Therapeutic Goods Administration

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