Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 4

Extract from the Clinical Evaluation Report for Tofacitinib citrate

Proprietary Product Name: Xeljanz

Sponsor: Pfizer Australia Pty Ltd

Date of CER:
Fourth round: 4 December 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About the Extract from the Clinical Evaluation Report

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

Contents

List of abbreviations

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

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

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

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

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

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

1. Introduction

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

The initial proposed indication was:

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

The Sponsor has amended the proposed indication to:

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

The submission initially proposed registration of the following dosage forms and strengths: tofacitinib citrate (JAQINUS / XELJANZ) 5 mg and 10 mg tablets.

The Sponsor now intends to proceed with registration of the 5 mg dose form only.

1.1. Overseas regulatory issues

See AusPAR Attachment 3 for issues related to refusal of the application by the EU CHMP.

1.2. Current submission

The Sponsor provided responses to issues raised by the CHMP which were addressed in a *Third Round Report* (see AusPAR Attachment 3). The Third Round report also generated some questions to the Sponsor, including a request for ECG data for Study A3921069 that had been omitted from the study report. The Sponsor provided the ECG data for Study A3921069 which was evaluated by the clinical Evaluator who responded [at Round 3] in a letter to the TGA (dated 2nd September 2013) with:

> "There appears to be one subject with prolongation of the QTc whilst taking tofacitinib 5 mg in Study A3921069. This resolved with dechallenge but did not occur with rechallenge. Overall, there were more subjects in the tofacitinib groups than with MTX with increase from baseline in both QTcB and QTcF of 30 to <60 ms and ≥60 ms at Month 12, but not at Month 24. At Month 12 there were 32 (10.9%) subjects in the tofacitinib 5 mg group, 33 (10.9%) in the 10 mg and 15 (12%) in the MTX with increase from baseline in QTcF of 30 to <60 ms. There were eight (2.7%) subjects in the tofacitinib 5 mg group, twelve (3.9%) in the 10 mg and one (0.8%) in the MTX with increase from baseline in both QTcF of ≥60 ms. At Month 12 there were 30 (10.0%) subjects in the tofacitinib 5 mg group, 22 (7%) in the 10 mg and 19 (14.8%) in the MTX with increase from baseline in QTcB of 30 to <60 ms. There were eight (2.7%) subjects in the tofacitinib 5 mg group, nine (2.9%) in the 10 mg and one (0.8%) in the MTX with increase from baseline in both QTcB of ≥60 ms. At Month 24 there were fewer subjects in the analysis, which may have excluded affected individuals from the Month 12 analysis.
>
> Although this is not a clear indication that tofacitinib is associated with prolongation of the QT interval, the risk benefit assessment was already marginal. This additional concern changes my assessment of the risk benefit and in my opinion more data are required before I could recommend approval for tofacitinib."

The Sponsor has responded to these concerns with additional data that will be addressed in the present report.

2. Clinical rationale

See CER Round 1 (AusPAR Attachment 2).

3. Contents of the clinical dossier

3.1. Scope of the additional clinical dossier

The additional data comprises:

- Response from the Sponsor
- Supporting Attachments
- Manuscript describing data from year 2 of Study A3921069
- Year 2 report from Study A3921044
- Individual patient data for subjects with QTc prolongation were provided for Study A3921069.
- Summaries of ECG changes for Study A3921019, Study A3921025, Study A3921035, Study A3921039, Study A3921040, and Study A3021045.
- Summaries of abnormal ECGs by visit for Study A3921019, Study A3921025, Study A3921035, Study A3921039, Study A3921040, and Study A3021045.
- Summaries of abnormal ECGs from monotherapy studies for up to 3 months
- Summary table of subjects with Torsades de pointes

3.2. Paediatric data

See CER Round 1 (AusPAR Attachment 2).

3.3. Good clinical practice

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

4. Pharmacokinetics

The additional data did not include any new pharmacokinetic data.

5. Pharmacodynamics

There were no new data relating to pharmacodynamics.

6. Dosage selection for the pivotal studies

There were no new data relating to dose finding studies.

7. Clinical efficacy

7.1. Efficacy in comparison with MTX

7.1.1. Pivotal efficacy studies

7.1.1.1. Study A3921069

A manuscript submitted to a medical journal reporting the Year 2 results for Study A3921069 was provided. This is discussed in Section 10 below.

7.1.1.2. Study A3921044

An updated study report describing the Year 2 for Study A3921044 was provided. This is discussed in Section 10 below.

8. Clinical safety

8.1. Studies providing evaluable safety data

- Individual patient data for subjects with QTc prolongation were provided for Study A3921069.
- Safety data were provided for Year 2 for Study A3921044.
- Summaries of ECG changes for Study A3921019, Study A3921025, Study A3921035, Study A3921039, Study A3921040, and Study A3021045.
- Summaries of abnormal ECGs by visit for Study A3921019, Study A3921025, Study A3921035, Study A3921039, Study A3921040, and Study A3021045.
- Summaries of abnormal ECGs from monotherapy studies for up to 3 months
- Summary table of subjects with Torsades de pointes

8.2. Post-marketing experience

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

8.3. Evaluator's overall conclusions on clinical safety

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

9. Clinical questions from round 3

9.1. Safety

- Were there any treatment emergent ECG abnormalities in Study A3921069?
- Have the safety data from Vaccine Substudy A3921024 previously been evaluated in Round 1 or 2?
- Has Study A3921152 reached completion and are the data available for evaluation?

- One case of potential DILI was referred to by the Sponsor in their response to the CHMP decision. Is this the same case referred to in the response to the Round 1 questions?

Evaluation of the sponsor response to the first question above appears below under *Fourth round evaluation of clinical data submitted in response to questions.* In addition, evaluation of the sponsor's response to all of the above questions appears in the addendum to the Delegate's initial Overview (see AusPAR).

9.2. Additional questions raised by the delegate

The following additional questions were raised separately by the Delegate in the initial Overview dated 29 August 2013 and Addendum dated 2 September 2013. The sponsor's responses to these questions are evaluated in the *Fourth round evaluation of clinical data submitted in response to questions*, below.

1. What concurrent medications was subject X taking at the time of the adverse event (Day 351), and at the time of recommencement (Day 371) and thereafter? Is there any known CYP3A4 interaction between any medications being taken concurrently at these times? Did the patient have any other abnormalities at the time of the adverse event eg abnormal liver functions tests, renal impairment? Did the patient have a history of any additional factors for QT prolongation? What were the QT intervals during other ECG recordings taken between recommencement (Day 371) and completion (Day 771. Is the patient still taking tofacitinib?
2. Did the subjects with QTc >500msec actually receive tofacitinib doses?
3. Are the patients with QTc >500msec at the 12-month analysis the same subjects who had the baseline recording >500msec at baseline?
4. How many patients developed a QTc >500msec while on either dose of tofacitinib?
5. What other timepoints were the ECGs taken and what were the results?
6. Did the patients who developed an increase in QTc prolongation >60msec or those who had an absolute QTc interval >500msec have any other additional risk factors for QT prolongation? Were they taking concomitant medications, or have hepatic or renal impairment, that might affect the metabolism or clearance of tofacitinib?
7. When will the complete 24-month ECG data for Study A3921069 become available?
8. What were the reasons for these patients terminating the study early?
9. The Sponsor is requested to explain why this ECG safety study data was presented at this late stage, and the reasons underlying this study being taken.
10. The Sponsor is requested to provide equivalent ECG data from the other pivotal efficacy studies.
11. The Sponsor is requested to provide a post-hoc analysis of equivalent ECG safety data across the entire safety database, plus any additional longer term data for ECG safety.
12. How many sudden deaths have there been in patients on tofacitinib?

10. Fourth round evaluation of clinical data submitted in response to questions

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

10.1. QTc prolongation

With regard the concerns of QTc prolongation, the Sponsor provided a response consisting of a general review of QTc prolongation and, presumably, expert opinion, although authorship of the document is not attributed. The Sponsor also states their interpretation of: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. The Sponsor also states that the thorough QT study for tofacitinib did not demonstrate QTc prolongation of regulatory concern, as has previously been noted by the Evaluator. The report ends with the following summary:

"In summary, there is no evidence of clinically relevant prolongation of the QT interval in the Phase 2 and 3 studies of the overall tofacitinib RA program. Furthermore the TQT study in healthy volunteers where the estimated adjusted mean difference was below 5 msec at all postdose time points has further confirmed that there is an absence of an effect on the QTc interval by tofacitinib. AEs coding to the SMQ were infrequent and balanced across treatment groups. And finally, in nonclinical studies at concentrations in excess of therapeutic concentrations, tofacitinib had no effect on hERG current or cardiac repolarisation in vitro or in vivo. Taken together, these data provide convincing evidence that tofacitinib treatment is not associated with an increase in the potential torsadogenic risk."

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

In response to specific questions regarding ECGs the Sponsor has responded:

TGA Question 1: What concurrent medications was [the] subject taking at the time of the adverse event (Day 351), and at the time of recommencement (Day 371) and thereafter? Is there any known CYP3A4 interaction between any medications being taken concurrently at these times? Did the patient have any other abnormalities at the time of the adverse event eg abnormal liver functions tests, renal impairment? Did the patient have a history of any additional factors for QT prolongation? What were the QT intervals during other ECG recordings taken between recommencement (Day 371) and completion (Day 771). Is the patient still taking tofacitinib?

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

TGA question 2: Did the subjects with QTc >500msec actually receive tofacitinib doses?

"A total of 8 patients had Screening QTcF values ≥500 msec: 3 patients each in the tofacitinib 5 mg and 10 mg groups, and 2 patients in the methotrexate group. All 8 patients received treatment."

The following data were provided for these subjects:

Table 1: Screening QTcF values ≥ 500 msec. Study A3921069

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

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

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

TGA question 3: Are the patients with QTc >500msec at the 12-month analysis the same subjects who had the baseline recording >500msec at baseline?

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

TGA question 4: How many patients developed a QTc >500msec while on either dose of tofacitinib?

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

The following summary tabulation was provided:

Table 2: Patients with QTc >500 msec while on either dose of tofacitinib. Study A3921069

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

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

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

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

Drugs known to affect QT were taken by six of the nine patients. Chloroquine or hydroxychloroquine were taken throughout the study by three patients; Bactrim (sulfamethoxazole/trimethoprim) was taken from day 713-722 by one patient, ofloxacin from days 178-182 and 633 to 637 by one patient, and mirtazapine daily regimen was started on day 451 for 1 patient. In the Evaluator's opinion, these concomitant medications could have been responsible for the QTc prolongation in these subjects.

None of these subjects discontinued because of QT prolongation.

TGA question 5: What other timepoints were the ECGs taken and what were the results?

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

For the first Subject, QTcF was 419 msec on Day -28, 483 msec on Day 351, 422 msec on Day 371 and 455 msec on Day 719.

For the other Subject, QTcF was 375 msec on Day -27, 441 msec on Day 85 and 417 msec on Day 99.

TGA question 6: Did the patients who developed an increase in QTc prolongation >60msec or those who had an absolute QTc interval >500msec have any other additional risk factors for QT prolongation? Were they taking concomitant medications, or have hepatic or renal impairment, that might affect the metabolism or clearance of tofacitinib?

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

TGA question 7: When will the complete 24-month ECG data for Study A3921069 become available?

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

TGA question 8: What were the reasons for these patients terminating the study early?

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

TGA question 9: The Sponsor is requested to explain why this ECG safety study data was presented at this late stage, and the reasons underlying this study being taken.

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

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

TGA question 10: The Sponsor is requested to provide equivalent ECG data from the other pivotal efficacy studies.

A summary of the electrocardiogram (ECG) data from other pivotal efficacy studies is provided in an attachment to the sponsor response: QTc/ECG Response. The 24 month ECG data from Study A3921044 is not summarized in the tables. For Study A3021045, at Month 6, the number (%) of subjects with an increase in QTcF from baseline ≥60 msec was eleven (4.9%) subjects for the 5 mg dose, nine (4.0%) for the 10 mg, one (1.8%) for the placebo to 5 mg and one (1.8%) for the placebo to 10 mg. These data do not raise any additional safety concerns.

TGA question 11: The Sponsor is requested to provide a post-hoc analysis of equivalent ECG safety data across the entire safety database, plus any additional longer term data for ECG safety.

A post-hoc analysis of the electrocardiogram (ECG) data across the clinical program is provided in an attachment to the sponsor response: QTc/ECG Response, and includes ECG data up to

Month 24 from study A3921069. The ECG data from Study A3921044 were not included. These data do not raise any additional safety concerns.

TGA question 12: How many sudden deaths have there been in patients on tofacitinib?

The Sponsor performed a search for any cases with reported fatal outcome that were received by Pfizer prior to 9 September 2013 in the combined data sets of the tofacitinib RA Phase 2, Phase 3, and long-term extension (LTE) studies. A total of 13 cases of sudden death that were possibly attributed to cardiac disorders were identified. After review, two cases were excluded, including one case with the event of death which occurred during the pre-randomization phase prior to treatment with study drug and one case where the patient was treated with adalimumab 40 mg every two weeks. The characteristics and descriptions of the remaining 11 cases were presented. All of these subjects appear to have underlying medical conditions that would have contributed to sudden death.

10.2. Post-hoc sensitivity analysis: joint progression

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

In the opinion of the Evaluator, these types of analyses might be useful in the design of Phase 3 studies, provided the assumptions used in the study are carefully scrutinised for plausibility, but are not evaluable for efficacy. The Sponsor also implies that Study A3921044 lacked the statistical power to demonstrate a significant effect on progression. Whilst the Evaluator agrees that Study A3921044 was underpowered, it is a convoluted argument to interpret this lack of power as supporting efficacy.

10.3. Efficacy with regard to structural progression

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

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

10.4. Relevance of structural findings in the context of the proposed second-line indication

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

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

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

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

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

10.5. Meta-analysis in support of safety

In their response the Sponsor has referred to a meta-analysis that they conducted in support of safety. The meta-analysis is purported to indicate that tofacitinib has a similar rate of serious infections, herpes zoster and malignancy as biological DMARDs. Although the Sponsor has provided tabulations and figures that demonstrate this in their response, and a description of the methodology for the study, the Evaluator has not been able to locate the report of this meta-analysis in the data provided for the Round 4 evaluation, or in previous tranches of data supplied by the Sponsor in support of tofacitinib.

10.6. RMP

The Sponsor is currently planning a post-approval comparative study with biological DMARDs (A3921133) that intends enrolling 4000 subjects.

10.7. Follow-up questions

A further four questions were submitted to the Sponsor in order to clarify aspects of the Fourth Round data (above):

TGA question: Please provide an update on the outcome (or end of study report, if this study has been completed) of Study A3921152 which addresses renal function while on

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

tofacitinib. If these data are not available, please state when this study was commenced and its completion date, and the planned timing of any interim reports.

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

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

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

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

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

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

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

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

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

11. Fourth round benefit-risk assessment

11.1. Fourth round assessment of benefits

After consideration of the responses to clinical questions, the benefits of tofacitinib in the proposed usage are unchanged from the *Third Round evaluation* (AusPAR Attachment 3); vis:

In addition to the benefits identified in Round 1 and Round 2, the additional data indicated benefit for tofacitinib 5 mg and 10 mg in comparison to MTX in subjects with active RA. In subjects with active RA, both tofacitinib 5 mg and 10 mg were superior to MTX, at doses of up to 20 mg weekly, for efficacy measures including joint preservation, for up to 12 months. The treatment effect was clinically and statistically significant. The statistical analysis was appropriate. In Study A3921069 there were 346 (93.3%) treated subjects in the tofacitinib 5 mg group, 369 (93.4%) for 10 mg and 166 (89.2%) in the MTX included in the analysis of mTSS. A higher drop-out rate in the MTX group would be supportive of efficacy. The secondary efficacy endpoints also strongly supported the primary efficacy analysis. The dose range for MTX was at the upper end of the recommended range for RA and was an appropriate comparator dose for assessing the efficacy of the tofacitinib doses.

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

11.2. Fourth round assessment of risks

After consideration of the responses to clinical questions, the benefits of tofactinib in the proposed usage are unchanged from the Third Round evaluation as stated in the *Third Round evaluation* (AusPAR Attachment 3); vis:

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

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

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

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

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

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

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

11.3. Fourth round assessment of benefit-risk balance

The benefit-risk balance is unchanged from the Third Round evaluation (AusPAR Attachment 3); vis:

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

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

- In the Round 3 Evaluation, the Sponsor was prepared to accept a third line indication for tofacitinib[2].
- The Sponsor has also been prepared to modify the indication in Europe and has stated: "*While Pfizer continues to believe that the preponderance of evidence supports use of tofacitinib as a second line therapy, the indication was modified specifically for the marketing authorisation application (MAA) in Europe based on feedback received during the review process and in an attempt to find a conservative, compromise position that would make tofacitinib initially available only to "third line" European RA patients with higher unmet medical need than "second line" patients.*"

Hence, the benefit-risk balance of Tofacitinib (CP-690,550), given the proposed third line usage, is favourable.

12. Fourth round recommendation regarding authorisation

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

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

The proposed indication does not reflect the status of tofacitinib as a third line agent[2].

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

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

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

13. Clinical questions from round 4

The Evaluator does not have any additional clinical questions.

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