26 January 2017
EMA/CHMP/853224/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xeljanz

International non-proprietary name: tofacitinib

Procedure No. EMEA/H/C/004214/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

Non Clinical abbreviations

ADME Absorption, distribution, metabolism, and excretion
AEs Adverse events
Ag Antigen
AIA Adjuvant induced arthritis
ALT Alanine aminotransferase
APA Action potential amplitude
APD Action potential duration
APD50 Action potential duration at 50% repolarization
APD90 Action potential duration at 90% repolarization
AST Asparate aminotransferase
AUC Area under concentration-time curve
AUC24 AUC from time 0 to 24 hours postdose
AUCt AUC from 0 to time t last postdose
BAT Brown adipose tissue
BCRP Breast cancer resistant protein
BID Twice a day
BP Blood pressure
bpm Beats per minute
BrDU 5-bromo-2'-deoxyuridine
BUN Blood urea nitrogen
BW Body weight
Ca Calcium
Cav Average steady state concentration
CaMK2α Ca2+/modulin-dependent protein kinase
CD16 Cluster of differentiation 16
CD4 Cluster of differentiation 4
CD8 Cluster of differentiation 8
CE Cholesterol ester
CHO Chinese hamster ovary
CIA Collagen induced arthritis
CL Clearance
Cmax Maximum (peak) observed drug concentration
Cmin Minimum observed concentration
CNS Central nervous system
CNTF Ciliary neurotrophic factor
ConA ConconavalinA
CRP C-reactive protein
CYP Cytochrome P isoenzyme
DA Dopamine agonist
DC Dendritic cells
DCAMKL3 Doublecortin and CAM kinase-like 3 kinase
DDI Drug-drug interaction
DEREK Deductive Estimation of Risk from Existing Knowledge
DNA Deoxyribonucleic acid
DMARD disease-modifying anti-rheumatic drug
DMSO Dimethyl sulfoxide
E Predicted extraction ratio
EBV Epstein Barr Virus
ECG Electrocardiogram
ED50 Effective dose, median
EFD Embryo-fetal development
EPO Erythropoietin
F Female
FACS Flourescent activated cell sorting

fu Fraction of drug free (unbound) in serum/plasma
GALT Gut associated lymphoid tissue
GD Gestation Day
GFR Glomerular filtration rate
GGT Gamma-glutamyltransferase
GLP Good Laboratory Practice
G-CSF Granulocyte Colony Stimulating Factor
GM-CSF Granulocyte-Macrophage Colony Stimulating Factor
HCT Hematocrit
HDL High density lipoprotein
HEK Human embryonic kidney
hERG Human ether- à -go-go related gene
HGB Hemoglobin
OATP Human organic anion transporting polypepetide
OCT2 Human organic cation transporter
hPBMCs Human peripheral blood mononuclear cells
hWB Human whole blood
HU03 Human erythro-leukemia cell line
IC50 50% inhibition concentration
ICH International Conference on Harmonisation
IFNα Interferon alpha
IFNγ Interferon gamma
Ig Immunoglobulin
IHC Immunohistochemistry
IL Interleukin
IV Intravenous
JAK Janus kinase
KCl Potassium chloride
Ki Inhibition constant
KLH Keyhole limpet hemocyanin
LC-MS/MS Liquid chromatorgraphy tandem mass spectrometry
LCV Lymphocryptovirus
LDL Low-density lipoprotein
LH Luteinizing hormone
LIF Leukemia inhibitory factor
LLNA Local lymph node assay
LOEL Lowest observed effect level
LPS Lipopolysaccharide
M Male
MAP Mean arterial blood pressure
MATE Multidrug and toxic compound extrusion
MDCK Madin-Darby canine kidney
MDR Multidrug resistance protein
MEC Molar extiniction coefficient
ML2 Melatonin receptor 2
MMF Mycophenalate
MPE Mean photo effect
mRNA Messenger RNA
MRP Multidrug resistance associated protein
MS Mass spectrometry
MTD Maximum tolerated dose
mWB Mouse whole blood
NA Not applicable
NADPH Nicotinamide adenine dinucleotide phosphate
ND Not determined
NE Norepinephrine
ng/mL Nanogram/milliliter
NK Natural killer
nM Nanomolar

NOAEL No observed adverse effect level
NOEL No observed effect level
NRU Neutral red uptake
NS No sample
OECD Organisation for Economic Cooperation and Development
OSM Oncostatin M
PBMC Peripheral blood mononuclear cell
P-gp P-glycoprotein
PIF Photo-irritancy factor
PL Plasma lipids
PK/PD Pharmacokinetic/Pharmacodynamic
PND Post natal day
PRL Prolactin
PTLD Post-transplant Lymphoproliferative Disorder
QD Once a day
QOD Every other day
QWBA Quantitative whole body autoradioluminography
RA Rheumatoid Arthritis
RBC Red blood count
RCT Reverse cholesterol transport
RMP Resting membrane potential
SAR Structure activity relationship
SC Subcutaneous
SCID Severe combined immunodeficiency
SI Stimulation index
STAT Signal transducer and activator of transcription
TC Total cholesterol
TCR T-cell receptor
TGF Tissue growth factor
TID Three times a day
TK Toxicokinetic
Tmax Time to reach peak concentration following drug administration
TNF Tumor necrosis factor
Treg Suppressor T cells
TyK2 Tyrosine kinase 2
UDS Unscheduled DNA synthesis
UGT Uridine diphosphate-glucuronyltransferase
US United States
UVA-UVB UltravioletA-UltravioletB
UVR Ultraviolet radiation
VEGF Vascular endothelial growth factor
Vmax Velocity of depolarization
Vss Volume of distribution at steady state
WBC White blood cell
WHO World Health Organization
WOCBP Women of childbearing potential

Clinical abbreviations

ACPA anti-cyclic citrullinated peptide antibodies
ACR American College of Rheumatology
ACR20 ACR criteria 20% response
ACR50 ACR criteria 50% response
ACR70 ACR criteria 70% response
AE Adverse Event
ACPA anti-cyclic citrullinated peptide antibodies or anti-citrullinated peptide antibodies
ADME Absorption, Distribution, Metabolism, Excretion
All RA Phase 2, Phase 3, and LTE studies
ALC absolute lymphocyte count

ATP Adenosine triphosphate
AUC Area under the concentration-time curve
BA bioavailability
BCC Basal cell carcinoma
BCS Biopharmaceutics Classification System
bDMARD biologic disease modifying anti-rheumatic drug
BE bioequivalence
BID Twice Daily
BL baseline
BMI body mass index
CDAI Clinical Disease Activity Index
CHMP Committee for Medicinal Products for Human Use
CI Confidence Interval
Cmax Maximum peak plasma concentration
CMI cell-mediated immunity
CMV Cytomegalovirus
CORRONA Consortium of Rheumatology Researchers of North America
COPD Chronic obstructive pulmonary disease
CK Creatine Kinase
CPK creatine phosphokinase
CRF Case Report Form
CRP C-Reactive Protein
CS corticosteroid
CSA Cyclosporine A
csDMARD Conventional synthetic disease modifying anti-rheumatic drug
CSR Clinical study report
CTLA4-IgG cytotoxic T-lymphocyte-associated protein 4 immunoglobin
CV Cardiovascular
CVD Cardiovascular disease
CYP Cytochrome P450
dL Decilitre
DAS Disease Activity Score Using 28 joint counts
DAS28-4(CRP) Disease activity score defined using 28 joint counts and CRP
DAS28-4(ESR) Disease activity score defined using 28 joint counts and erythrocyte sedimentation rate
DBP Diastolic blood pressure
DC discontinuation
DILI drug-induced liver injury
DMARD Disease modifying anti-rheumatic drug
EMA European Medicines Agency
EPO Erythropoietin
ESR Erythrocyte Sedimentation Rate
EU European Union
EULAR European League Against Rheumatism
FACIT-fatigue Functional Assessment of Chronic Illness Therapy-Fatigue scale
FDA Food and Drug Administration
GC glucocorticoids
HAQ-DI Health Assessment Questionnaire Disability Index
Hb haemoglobin,
HCP healthcare provider
HDL High Density Lipoprotein
HN hypertension
HZ Herpes Zoster
ICH International Committee on Harmonization
IFN interferon
IL Interleukin
INH isoniazid
IR Inadequate responder
IR Incidence rate
IgG Immunoglobulin G

IV Intravenous
JAK1 Janus Kinase 1
JAK2 Janus Kinase 2
JAK3 Janus Kinase 3
LDA low disease activity
LDL Low Density Lipoprotein
LDL-c Low Density Lipoprotein - Cholesterol
LEP Linear extrapolation
LSC Lymphocyte subset count
LTE Long-term extension
MAA Marketing Authorisation Application
MACE Major adverse cardiovascular event
MCID Minimum clinically important difference
MCS/PCS mental component summary/ physical component summary
MedDRA Medical Dictionary for Regulatory Activities
MMF Mycophenolate mofetil
MOA mechanism of action
MTX Methotrexate
MTX-IR Methotrexate-inadequate responder
mTSS modified Total Sharp Score
NHL non-Hodgkin's lymphoma
NMSC nonmelanoma skin cancer
NK natural killer
NSAID(s) Nonsteroidal Anti-Inflammatory Drug(s)
PBO placebo
PD Pharmacodynamics
PK Pharmacokinetic
PRAC Pharmacovigilance Risk Assessment Committee
PRL prolactin
PRO patient reported outcomes
PT Preferred Term
PT LD post-transplant lymphoproliferative disorder
PY patient-year
OI opportunistic infection
QD Once daily
QOW Every other week
QT Interval from the beginning of the QRS complex to the end of the T wave
RA Rheumatoid arthritis
RCT randomized controlled trial
RF Rheumatic factor
RMMs risk minimisation measure
RMP Risk Management Plan
SAE Serious adverse event
SBP Systolic blood pressure
SC Subcutaneous
SCC Squamous cell carcinoma
SCE Summary of Clinical Efficacy
SCID severe combined immunodeficiency
SCP Summary of Clinical Pharmacology
SCS Summary of Clinical Safety
SDAI Simplified Disease Activity Index
SEER Surveillance Epidemiology and End Results
SF-36 Short Form 36 Health Survey
SI serious infection
SIR Standardised incidence ratio
SmPC Summary of Product Characteristics (EU)
SMQ Standardised MedDRA query
SOC System Organ Class
STAT Signal Transducer and Activator of Transcription

SAWP Scientific Advice Working Party
TB tuberculosis
TC Total cholesterol
TEAE Treatment Emergent adverse event
TNFi Tumour Necrosis Factor inhibitor
TyK2 tyrosine kinase 2
ULN upper limit of normal
US United States
UTI urinary tract infection
VZV Varicella-zoster virus
WHO World Health Organisation
YLD Years living with disability

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Limited submitted on 3 March 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for XELJANZ, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 April 2015.

The applicant applied for the following indication:

XELJANZ in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have had an inadequate response to MTX. XELJANZ can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate. XELJANZ, alone or in combination with MTX, has shown improvements in physical function.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that tofacitinib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision/0013/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0013/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance tofacitinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 8/01/2015, 14/04/2011, 22/01/2009, 12/02/2009. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 3 March 2016.
- The procedure started on 24 March 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 June 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 June 2016 . The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 28 June 2016 .
- During the meeting on 21 July 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 July 2016 .
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 October 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 November 2016 .
- During the PRAC meeting on 1 December 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 1 December 2016 .
- During the CHMP meeting on 15 December 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant .
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 December 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 11 January 2017 .
- During the meeting on 23-26 January 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Xeljanz.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

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

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease that causes progressive damage to small and large joints (termed structural progression).

2.1.2. Epidemiology and risk factors

Rheumatoid arthritis is a common disease with a prevalence of 0.5 – 1.0% and occurs 2 -3 times more commonly in women than men although the gender difference becomes less pronounced, the later the age of onset. The incidence rises with age and peaks between 65 and 74 years of age. The underlying cause is still unknown but is thought to result from a complex interplay of genetic and environmental factors. The disease is characterised by structural joint damage accompanied by pain and swelling, causes progressive disability, can result in early death and brings socioeconomic burdens.

The natural history of RA varies considerably and has at least 3 possible disease courses:

1. Monocyclic associated with one episode only that ends within 2-5 years of initial diagnosis
2. Polycyclic: the levels of disease activity fluctuate over the course of the condition
3. Progressive: the disease is steadily progressive and does not fluctuate

2.1.3. Biologic features

RA is an autoimmune disease, involving activation of several immune cell subsets: T cells with release of T-cell-derived cytokines, production of autoantibodies (rheumatoid factor and anti-citrullinated protein antibody (ACPA) by B cells, and also involves macrophage and fibroblast-like cells which secret large amounts of pro-inflammatory cytokines.

2.1.4. Clinical presentation, diagnosis

RA is characterised by synovial inflammation and hyperplasia (“swelling”), autoantibody production, cartilage and bone destruction leading to deformity. It is also often associated with systemic complications arising from vasculitis together with cardiovascular and pulmonary complications.

Changes to joints are characterised by synovial inflammation and hyperplasia, followed cartilage and bone destruction leading to deformity. Erosive changes in the peri-articular bone typically occur early in the first year of disease. There is a drive to earlier diagnosis of RA so that disease-modifying therapy can be commenced early.

The diagnosis is a clinical one, based on physical examination, serology and X-rays. The presence of joint erosions is *prime facie* evidence of RA but RA can be diagnosed on the basis of seropositivity (positive rheumatoid factor and/or anti- citrullinated peptide) in the absence of X-ray evidence of joint involvement. The American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) classification criteria help to define level of severity and disease prognosis so that treatment decisions can be informed.

2.1.5. Management

Available therapies for rheumatoid arthritis range from treatments that largely provide symptom relief, such as NSAIDs, to a number of conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), the folate antagonist methotrexate (MTX) being the cornerstone. Other csDMARDs including leflunomide and sulphasalazine can be used as alternatives or in combination with MTX. More recently, a range of biological therapies (bDMARDs) that target the innate and adaptive immune response pathways, including anti-TNF, anti-IL-1, anti-IL-6 and B cell depleting agents have been developed. Biological therapies authorised in Europe for the treatment of rheumatoid arthritis include a number of TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab); the T cell stimulation inhibitor abatacept; the B cell depleting agent (anti-CD20 antibody) rituximab; IL-6 receptor blocking antibody tocilizumab; and the IL-1 inhibitor anakinra.

Patients exhibit varying responses to biological therapies and can acquire resistance. Adverse effects due to immunocompromise and the need for systemic administration are drawbacks also. Nonetheless, these newer generation therapies can be highly effective and have shifted the expectation for clinical outcome using a “treat to target” approach that aims for remission or, at minimum, low disease activity. If sustained, these outcomes can be correlated with slowing of progression of joint damage although this is not always the case and structural progression can continue despite suppression of signs and symptoms. Due to the effectiveness of biological therapies and a safety profile that is generally acceptable in light of the efficacy benefit, these agents are now considered as standard second line treatment in rheumatoid arthritis where patients have failed to respond to one or more csDMARDs, usually methotrexate. Biological therapies are also given as third line treatment after failure of a previous line of biological therapy, even if this is targeted to the same pathway (as with the TNF inhibitors).

Inhibition of structural damage is considered the ultimate goal in therapy for RA. Clinical practice guidance in Europe and the US advocates a treat to target approach – aiming for remission or low disease activity as measured by composite scores of disease activity. The use of stringent composite scores of disease activity is encouraged.

In the management of RA in the second line treatment setting (MTX-IR or other csDAMRD-IR patients), where the standard of care is biological DMARD therapy, background MTX is generally continued even in patients who are inadequately responsive to MTX. This is recommended in the 2013 ACR/EULAR guidance on the grounds that no biologic DMARD as monotherapy has shown superior efficacy over a bDMARD in combination with MTX and the side effect profile is manageable. Presumptively there is enhanced anti-

inflammatory and/or immunomodulatory activity although suppression of anti-drug neutralising antibodies by MTX has also been invoked as a contributor in some cases.

About the product

Tofacitinib has been developed as an oral, immunomodulatory disease-modifying anti-rheumatic drug (DMARD) to treat rheumatoid arthritis. It is a synthetic molecule that selectively inhibits the JAK kinase family, unlike the available biological therapies that target TNF, specific interleukins or lymphocyte cell surface antigens

JAK kinases act as intracellular transducers of signals from diverse extracellular cytokines. Tofacitinib has high specificity for the JAK kinase family within the human kinome and inhibits all four JAK family members with rank order of potency JAK3>JAK1>JAK2>Tyk2. In the cellular context, where JAKs form heterodimeric complexes on the inner aspect of the cell surface membrane, tofacitinib preferentially inhibits JAK3/JAK1 heterodimers.

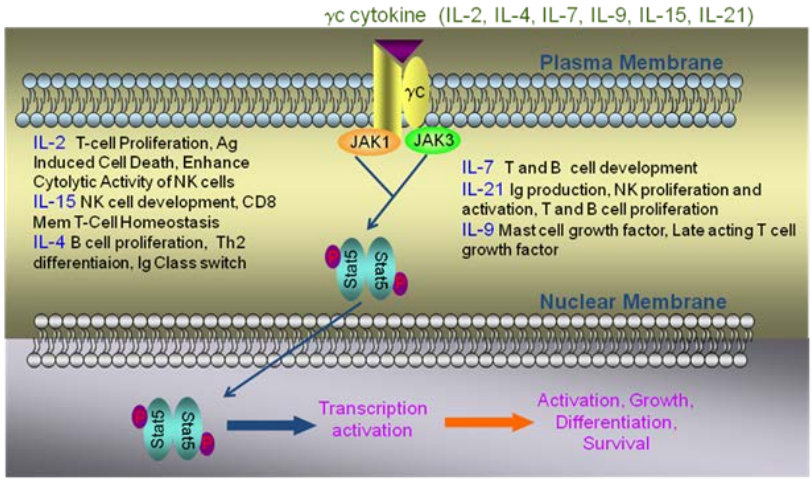
Although JAK3 only pairs with JAK1 to mediate common γ chain cytokine signalling, JAK1 also pairs with JAK2 and TyK2 to transmit signals from additional cytokines important in inflammation and immune responses including IL–6, IFNα and IFNγ (Figures 1 and 2). JAK2 homodimers are critical for the signalling of hematopoietic cytokines and hormones including (erythropoietin) EPO, IL-3, granulocyte/macrophage colony stimulating factor (GM-CSF), prolactin, leptin, and growth hormone. TyK2 pairs with JAK1 to mediate multiple cytokine pathways including IL 10 and type I interferons; IL 12 and IL 23 are dependent on Tyk2 and JAK2 for transmitting their signal.

In rheumatoid arthritis, cytokine dysregulation is manifest as overproduction of a number of proinflammatory cytokines including (IL)-1, IL-6, IL-8, IL-15, IL-17, IL-18, IL-23 and tumour necrosis factor-alpha (TNFα). A therapeutic strategy that targets a key downstream transducer of diverse signalling molecules is therefore logical.

Notably, the JAKs do not directly transduce signals from the TNF family and therefore TNF inhibitors used in the treatment of rheumatoid arthritis act via a different primary signalling pathway. That said, cross-talk between the JAK-STAT and MAPK/SAPK pathways (activated by additional cytokines that do not directly activate the JAK pathway) can also occur and therefore targeting the JAK-STAT pathway has potential for wide-reaching effects. JAK can therefore be considered to sit at a nodal point in the complex network of cytokine signalling.

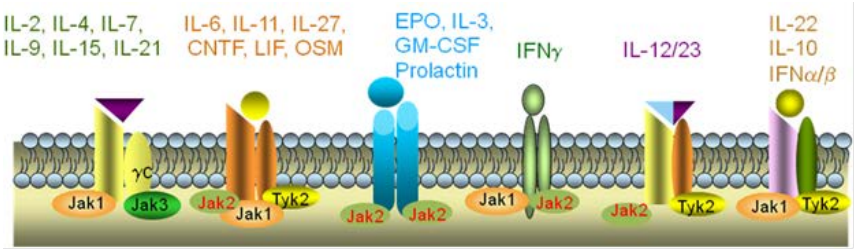
Upon binding of the cytokine to its receptor, the associated JAKs become transactivated and co-recruit and activate signal transducer and activator of transcription (STAT) family of transcription factors. The STAT complexes translocate to the nucleus where they bind to specific gene promoters to activate transcription of a range of target genes.

Figure 1 - Schematic Diagram of the JAK1/3 Signalling Pathway



Ag = Antigen; γc = Common gamma chain; Ig = Immunoglobulin; IL = Interleukin; JAK = Janus Kinase; NK = Natural killer; P = Phosphate; STAT = Signal transducer and activator of transcription.

Figure 2 - Receptor pairing within the Janus kinase family



CNTF = Ciliary neurotrophic factor; EPO = Erythropoietin; γc = Common gamma chain; GM-CSF = Granulocyte/macrophage colony stimulating factor; IFN = Interferon; IL = Interleukin; JAK = Janus kinase; LIF = Leukemia inhibitory factor; OSM = Oncostatin M; STAT = Signal transducer and activator of transcription; TyK = Tyrosine kinase.

Claimed indication:

XELJANZ in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have had an inadequate response to MTX.

XELJANZ can be given as monotherapy in case of intolerance to MTX or when continued treatment with MTX is inappropriate.

Approved indication:

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

The recommended dose is 5 mg administered twice daily.

Type of Application and aspects on development

The application has been submitted in accordance with Article 8.3 of Directive 2001/83/EC and consists of a complete dossier with administrative, quality, non-clinical and clinical data. The eligibility for submission

through the Centralised Procedure (CP) under Article 3(1) – Indent 3 of Regulation (EC) No 726/2004 (new active substance, mandatory scope) was confirmed by the EMA on 23rd April 2015 (EMEA/CHMP/268028/2015).

Tofacitinib 5 mg b.i.d. is approved as 2nd line therapy for the treatment of adults with moderate to severe RA in 45 countries and marketed in 29 countries worldwide including the United States, Canada, Switzerland, Australia and Japan. Tofacitinib 10 mg b.i.d. is also approved for the treatment of RA in 3 countries (Switzerland, Russia, and Botswana).

On 27th October 2011, the Applicant submitted a Marketing Authorisation Application (MAA) via the centralised procedure for tofacitinib for the treatment of moderate to severe RA in adults as a 2nd line agent. During the procedure, the indication was modified to 3rd line (in patients inadequately responsive to one or more biological therapies). CHMP adopted a negative opinion on 25th April 2013, following which the Company requested a re-examination. During the re-examination an ad hoc expert meeting was convened on 15th July 2013 to consider the issues. The Applicant addressed the detailed grounds for re-examination at an oral hearing during the CHMP meeting on 22nd July 2013. A final negative opinion was concluded by a majority decision (19 negative, 13 positive) during the CHMP meeting 22 – 25 July 2013.

> The 3 major grounds for refusal were:
>
> **Ground One:**
>
> 'There are significant and unresolved concerns regarding the number of serious and opportunistic infections observed with tofacitinib in the clinical studies, which are indicative of impaired cell-mediated immunity. These risks are related to the primary pharmacology of this first in class agent. The clinical development programme has limitations as it did not adequately characterise these risks; relevant information from the toxicological program was not adequately followed-up in the clinical development program leading to uncertainties in mechanistic understanding.'
>
> **Ground Two:**
>
> 'The overall safety profile, and the uncertainties relating to safety, remain of major concern, in particular the incidence and severity of infections, malignancies, lymphoma, gastro-intestinal perforations, hepatic enzymes elevations/drug-induced liver injury and lipids and cardiovascular risks. There are limited safety data in the proposed patient population and a lack of reassurance that the available data from other patient populations in the clinical trial programme is fully applicable. Consequently, there are uncertainties surrounding the magnitude of the severe risks and their management in clinical practice.'
>
> **Ground Three**:
>
> 'The unresolved concerns regarding the safety profile and the uncertainties relating to safety are not offset by the benefits of treatment, that are in addition not supported by robust evidence on the prevention of structural damage at the proposed dose [5 mg B.I.D.] in the proposed treatment population [ie, patients who have had an inadequate response or are intolerant to previous therapy with at least one biological DMARD].'

The applicant has revised the dossier, which includes additional studies, to address the concerns raised during and at the conclusion of the previous procedure.

The pivotal clinical studies were designed in line with the available CHMP and FDA guidance for clinical development of medicinal products in RA at the time : "Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDs for Treatment of Rheumatoid Arthritis" (CPMP/EWP/556/95 rev 1/

Final, December 2003) and the US FDA “Guidance for Industry: Clinical Development Programmes for Drugs, Devices, and Biological Products for the Treatment of Rheumatoid Arthritis” (February 1999). A revision of the previous EMA guideline on clinical development of medicinal products for RA has been released in draft form (CPMP/EWP/556/95 rev2).

EMA Scientific Advice was sought by the company following completion of the initial and re-examination MAA procedures.

November 2014: CHMP scientific advice procedure EMA/136669/2014 in relation to the planned pre-approval data package. CHMP advised that the proposed updated EU MAA package including the increased exposure/safety data could be considered appropriate to support an EU MAA submission. The final CHMP advice recommended that a target population representing the majority of the tofacitinib Phase 3 development study population and one that reflects EU treatment practices should be proposed in the new EU MAA submission. One non-compliance detected was failure to include an active comparator the second line indication in a powered study.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 5 mg of tofacitinib (as tofacitinib citrate) as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate.

Film coat: hypromellose 6cP (E464), titanium dioxide (E171), lactose monohydrate, macrogol 3350, and triacetin (E1518)

The product is available in HDPE bottles with silica gel desiccant and child-resistant caps and aluminium foil/PVC backed aluminium foil unit dose blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of tofacitinib citrate is 3-((3*R*,4*R*)-4-methyl-3-(methyl(7*H*-pyrrolo[2,3-d]pyrimidin-4 yl)amino)piperidin-1-yl)-3-oxopropanenitrile, 2-hydroxypropane-1,2,3-tricarboxylic acid corresponding to the molecular formula $C_{16}H_{20}N_6O$ and has a relative molecular mass 312.49 g/mol and the following structure:

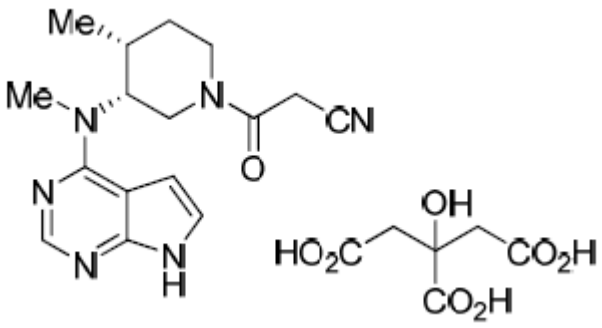


Figure 3 – Structure of tofacitinib citrate

The chemical structure of tofacitinib has been adequately demonstrated by UV spectroscopy, infrared (IR) spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, elemental analysis, mass spectrometry, and X-ray crystallography.

The active substance is a white to off-white solid, slightly soluble in water and non-hygroscopic.

Tofacitinib contains two chiral centres at C3 and C4. The active substance is the enantiomer with absolute configuration (*R*) for both the C-3 and the C-4 positions. The overall stereochemistry of tofacitinib is therefore considered as critical and is assured by the quality of the starting materials and the route of synthesis design.

Polymorphism has been studied for the active substance. The crystalline citrate salt, Form A, has been the sole development form of the active substance used in all toxicology and clinical studies

Manufacture, characterisation and process controls

Tofacitinib is supplied by one active substance manufacturer. The synthesis of tofacitinib citrate consists of four chemical transformations in three steps. Well defined starting materials with acceptable specifications are used.

The manufacturing process is well described. The process description clearly indicates the in-process controls and target conditions. Reworking is proposed and is considered acceptable on the basis that the method of recrystallization is virtually a repetition of the last crystallisation step of the main process and no additional solvent systems are used.

A Quality by Design (QbD) approach to the process development and manufacture of the active substance has been applied.

The applicant presented detailed data on risk assessment, criticality of each step of manufacture using Failure Mode Effect Analysis (FMEA) and high resolution design of experiments (DoEs) for steps 1 and 2 and sub-steps 3 along with their statistical analyses. Both the critical and noncritical process parameters were clearly identified alongside their ranges. The conclusions of these DoEs generally support the ranges of critical process parameters (CPPs) and non CPPs described. Based on the studies, design spaces have been proposed for step 1 and step 3 of the synthesis. The design spaces were established with lab scale batches. For the steps which are not part of the design space, proven acceptable ranges have been specified. The active substance critical quality attributes (CQAs) and the control strategy have been adequately described.

Data from five batches (4 commercial and 1 technical transfer batch) of tofacitinib produced by the commercial process at the corresponding manufacturing site were presented. All test results are comparable to those obtained for the clinical trial batches, with no significant trend observed.

Taking into account the experience gained during manufacture of clinical and registration stability batches and the control strategy, it can be considered that the design space has been verified at commercial scale when operating within the NORs. In addition, the applicant submitted a justification which includes the identification of scale dependent and independent parameters that drive the lifecycle approach to design space verification. In addition, although the DOE work was performed on laboratory scale, the trends and correlations revealed through this experimental work were consistent with the outcomes of pilot plant and commercial validation campaigns. Additional verification at scale will be conducted as appropriate in line with the design space verification strategy, whenever process changes within the approved design space are needed. This was considered satisfactory.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

This packaging material is standard for the packaging of active substance and complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description, identification (IR, Chiral LC), particle size, assay (LC), counterion of citric acid (LC), impurities (LC), residue on ignition (USP), heavy metals (USP), residual solvents (GC), water content, palladium (ICP-OES).

The active substance specifications are based on the active substance critical quality attributes (CQA). The CQAs identified are identification, particle size, assay and impurities.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis data have been provided for 43 batches of the active substance. These batches were used for development, stability studies and for the manufacture of finished product used in clinical studies and for commercial purposes. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturer and three supportive commercial scale batches from another manufacturer stored in the intended commercial

package for 36 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Photostability testing following the ICH guideline Q1B was performed on one batch.

Results on stress conditions under acid, base, oxidation, thermal, thermal/humidity and light) were also provided in one batch.

The following parameters were tested*:* appearance, assay, impurities, water content, chiral purity, and microbial contamination. The analytical methods used were the same as for release and were stability indicating.

The active substance stored under long term and accelerated conditions proved to be stable for all the parameters tested. No trends in the formation of impurities were noticed. The microbial quality was maintained for the entire storage period.

In relation to the photostability testing, all results met the specification with no significant changes compared to the initial results. Therefore, the active substance is not light sensitive.

Regarding the stress conditions, the active substance was sensitive to all the stress conditions in particular to basic hydrolysis, acidic hydrolysis and oxidation.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as a white, round, biconvex film-coated tablet, debossing “Pfizer” on one side and “JKI 5” on the reverse, containing tofacitinib (as tofacitinib citrate) as active substance.

The formulation development was based on a QbD approach: the quality target product profile (QTPP) was defined as white, round, immediate-release film-coated tablets suitable for oral administration, twice daily, to adult patients containing 5 mg of tofacitinib that meet compendial and other relevant quality standards, and is packaged in blisters and bottles.

The critical quality attributes (CQAs) identified were appearance, identification, assay, degradants, uniformity of dosage units, disintegration, microbial limits, and water content.

The active substance is a non-hygroscopic, white to off-white solid, and is classified as BCS Class III compound. As mentioned above, it is synthesized as a citrate salt and Form A is the only crystalline form identified. Polymorphism screen was performed. Form A was used for product development and clinical supplies manufacture, and will be used in commercial manufacturing.

To assess the impact of active substance particle size on uniformity of dosage units, mathematical modeling, development scale multivariate experiments, and pilot/production scale manufacturing experience were used. The modelling approach proposed to define the active substance particle size acceptance criteria was confirmed to be accurate, and was verified by experimental data for tofacitinib tablets and several other similar products. Data from the peer-reviewed literature supported this position and suggested that the proposed active substance particle size limits were conservative. The sensitivity of the output to the

assumptions of the model and the input parameters were evaluated and the output from model was considered to be robust to such changes.

The selection of the excipients for the Phase 3 clinical studies and the commercial formulation (namely, microcrystalline cellulose, lactose anhydrous, croscarmellose sodium, and magnesium stearate) was based on data from a 6 week open dish accelerated stability study using different blends of excipients and active substance. During the course of development, lactose anhydrous and monohydrate were used in the manufacture of tablets for Phase 2 clinical studies. Both grades of lactose were found to have similar compatibilities with the active substance. The lactose monohydrate was selected for the Phase 3 clinical studies and commercial formulation based on prior experience with this excipient. The choice of the commercial coating system was also based on compatibility of the various coating materials with the active substance. A film-coating system was selected based on the more favourable results of an open dish study performed at accelerated conditions. The function of each excipient has been outlined and is appropriate. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

An oral powder for reconstitution was used for Phase 1 clinical studies. Additionally, an IV formulation was developed to support the absolute bioavailability study. The immediate release tablets were developed and utilized in the later phases of development. These tablets were uncoated for Phase 2 clinical studies, and film coated for Phase 3 clinical studies and commercial supplies. A material risk assessment was conducted to identify which active substance and excipient properties could potentially impact finished product quality or the manufacturing process. Active substance particle size, raw material water content, and excipient batch to batch variability were identified as potentially important formulation factors.

The film-coated tablets are an immediate release (IR) formulation designed to disintegrate and dissolve rapidly under physiological conditions in the stomach. A justification for using disintegration as the performance test for the finished product instead of dissolution test was provided by establishing a correlation between them. The active substance is classified as a BCS class III compound, indicating that solubility is not the rate limiting factor for bioavailability. Moreover, the solubility profile, dissolution studies performed in different conditions (apparatus, agitation speed) across the physiological pH range, and disintegration studies support the rapid dissolution of active substance following rapid disintegration of the finished product. It was acknowledged that the disintegration time is a more relevant quality attribute (QA) than dissolution, and a slightly more discriminating test for the finished product. In view of this, the ICH Q6A, and considering the demonstrated relationship between disintegration and dissolution, testing disintegration time at release in lieu of dissolution was considered acceptable.

The commercial tablets are manufactured by a conventional dry granulation process, using equipment commonly available in the pharmaceutical industry.

During pharmaceutical development, a FMEA was conducted to establish the critical and non-critical quality attributes of the finished product. This assessment considered the quality target product profile (QTPP), the biopharmaceutical properties of the active substance, and prior manufacturing experience. Focus areas (FA) were then defined, and a cause-and-effect analysis was performed on each focus area to assess the potential impact of the process parameters and upstream material properties on the quality attributes listed in the QTPP. Following each risk assessment, a comprehensive experimental plan was developed to study selected process parameters in each of the focus areas utilizing multivariate and univariate experiments, as well as engineering models. The goal of these studies was to generate the knowledge space that could be used to establish the design space. Uniformity of dosage units and the level of degradants observed during stability

studies were identified as the critical quality attributes (CQA) of the finished product that could be impacted by the formulation or manufacturing process. A series of statistically designed studies revealed the functional relationships between the process parameters and these two CQAs. The knowledge gained from these studies, in conjunction with prior experience, provided the basis for designating the critical process parameters (CPP), the key process parameters (KPP) and the non-critical process parameters (non-CPP). The 3-tier system was later changed to a 2-tier system (CPPs /non-CPPs only) to be aligned with the terminology defined by ICH Q8.

The primary packages are HDPE bottles with silica gel desiccant and child-resistant caps or aluminium foil/PVC backed aluminium foil unit dose blisters. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 10 main steps. In summary, the excipients are blended, dry granulated and then compressed to form the tablet core. The core is then film-coated with opadry and packed into the proposed container closure system. The process is considered to be a standard manufacturing process.

The manufacturing process development was based on a QbD approach and designed to consistently meet the quality attributes, which were derived from the finished product profile.

Among the multivariate studies performed, four DoEs, conducted at development scale, are described in the dossier: two screening DoEs (fractional factorial, resolution III, multivariate studies) to identify critical process parameters (CPP) and their acceptable ranges; two additional DoEs (fractional factorial, resolution V and IV, multivariate studies) to explore dry granulation and compression processes in greater depth. Adequate information regarding statistical analysis has been provided.

At the end of the development section, the applicant defines a design space covering dry granulation and milling parameters.

To verify and validate the design space, two technology transfer (TT) commercial scale batches were manufactured at the commercial site. The two TT batches were successfully manufactured and all quality attributes met specification requirements for the finished product. Additionally, in-process testing for the evaluation of uniformity of dosage units, water content, and efficiency of compression process (such as dwell time and compression force) were conducted. Following the initial design space verification for the process parameter ranges and target settings, conventional process validation was successfully completed for the finished product manufacturing with the process NORs according to a pre-approved process validation protocol provided.

The design space verification protocol provided for finished product is considered satisfactory. The approach proposed to evaluate any change to the manufacturing process within the design space and its impact on the control strategy and the quality of finished product is endorsed. The additional tests proposed for each attribute/parameter movement within design space, as a function of finished product quality attributes that can be impacted, are found adequate.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (UV, LC), assay (LC), uniformity of dosage units (LC), individual specified degradation products (LC), individual unspecified degradation products (LC), total degradation products (LC), disintegration (Ph. Eur.), water content (KF), microbial limits (Ph. Eur).

As mentioned above, a justification for using disintegration as the performance test for the finished product instead of dissolution test was provided. This was considered satisfactory.

The justification for the removal of the test for chiral purity was considered acceptable as the stability data demonstrated no increase of the enantiomer throughout the 12 months long-term and 6 months accelerated conditions. Furthermore, it was demonstrated that the enantiomeric impurity is a process related impurity as opposed to a degradation impurity. Therefore subject to the enantiomer being suitable controlled within the active substance there is no necessity for this impurity to be controlled within the finished product.

Regarding the polymorphic form of the active substance, no specific control has been included in the active substance specification. This is acceptable on the basis that it is demonstrated that the polymorphic form remains the same throughout the shelf-life of the finished product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. No additional reference standards or materials are used for the testing of the finished product other than those of the active substance.

Batch analysis results are provided for 78 pilot and commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing

Stability of the product

Stability data on three pilot scale batches of finished product stored for 36 months under long term conditions at 25 ºC / 60% RH and and 30°C/75% RH and, for up to 6 months under accelerated conditions at 40 ºC / 75% RH, according to the ICH guidelines, were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay and degradation products, water content, dissolution, chiral purity, disintegration and microbiological quality. The analytical procedures used are stability indicating.

The foil/foil blister is actively tested for all batches. A bracketing design is applied to the testing for the HDPE bottle packages. Two HDPE bottles (6 and 180 count with desiccant) that bracket the moisture vapour transmission rate (MVTR)/unit range are actively tested during the registration stability program.

No trends or out of specification results were observed in the batches stored at long term or accelerated conditions. Moreover, no discernible differences between the two different container closure systems were observed.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes were observed in any of the parameters measured. Therefore, no precautionary packaging or labelling is required.

An in-use open dish study was conducted to establish the in-use shelf life after opening of the finished product packaged in bottles. The samples were stored in an open dish for one month. The samples were tested during this period. No significant changes were observed in any of the parameters measured. As expected, the exposed finished product absorbed moisture. Moisture levels up to 6.8% followed by a plateau were observed. The increase did not impact stability, quality or performance of the product as measured by the other tested attributes, and the data support a one month in-use shelf life.

Forced degradation studies were also performed. Samples were stressed under a variety of conditions including thermal, thermal with humidity, oxidative (in solution) and light exposure. Samples were analysed for potency and degradation products by LC as well as peak purity utilizing photo diode array (UV). Overall the finished product showed resistance to oxidative and thermal conditions. Some degradation was observed under increased humidity levels.

Based on available stability data, the proposed shelf-life of 36 months with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. Design spaces have been proposed for several steps in the manufacture of the active substance and finished product. The design spaces have been adequately verified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical safety pharmacology package was conducted and completed prior to finalization of the ICH S7 (June 2001), and as such not specifically under full GLP conditions. The Applicant stated that study designs are in accordance with current ICH guidelines and were conducted to high quality standards and scientific principles: this was considered sufficient by SAWP (EMEA/H/SA/1219/1/2008/III).

The applicant states that the non-clinical data submitted in support of this application (EMEA/H/C/4214) is essentially the same as that submitted for the previous application (EMEA/H/C/2542).

Calculation of the safety margins has been updated on the basis of the clinical dose of 5 mg twice daily: the Cmax was determined to be 58 ng/mL and the AUC24 was 507 ng•h/mL. The mean fraction unbound in human plasma of tofacitinib was determined to be 0.61 and used to calculate unbound Cmax (35 ng/mL) and unbound AUC24 (309 ng•h/mL) values.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Tofacitinib showed selectivity for Janus kinase with IC_{50} of 3.2, 4.1 and 1.6 nM for JAK1, 2 and 3 respectively. The affinity for TyK2 was lower with an IC_{50} of 34 nM. All other tested kinases had IC_{50} >1 µM. In cellular models, tofacitinib confirmed its selectivity for JAK1/3 and in a lesser extent for JAK2.

In the mouse collagen-induced arthritis, tofacitinib decreased plasma cytokines (IL-6) levels when administered as a preventive treatment. As a curative treatment, tofacitinib reduced arthritis symptoms and histological signs of inflammation. However, it induced no decrease in cartilage damage or inhibition of pannus formation. Treatment-related changes in STAT1 responsive genes were observed. Gene sets corresponding to macrophage, B cells, T cells and osteoclasts were repressed and genes associated with NK cells were suppressed. A PK/PD modelling revealed that effective inflammation modulation leading to arthritis efficacy through JAK1/3 inhibition may not require continuous coverage of the target over the day, but could be more related to an optimal on and off target effect.

In the rat adjuvant-induced arthritis, when treatment started prior disease development, tofacinitib dose-dependently reduced hind paw volume and neutrophil counts along with a decrease of IL-6, IL-17 and α2-macroglobulin and a an increase in cholesterol.

When administered after arthritis development, it reduced hind paw volume, neutrophil count and cytokines (IL-6, IL-17, α2-macroglobulin). It inhibited bone resorption and CD68 and CD3+ cells infiltration but no effect on pannus formation or cartilage destruction was observed. Gene sets corresponding to macrophage, B cells, T cells and osteoclasts were repressed and genes associated with NK cells were suppressed.

In rodent arthritis models, tofacitinib showed an effect on the decrease of inflammatory endpoints (decrease of cytokine levels in plasma and arthritic tissue) and on bone resorption but it had no effect on cartilage destruction.

Tofacitinib increased the rate of reverse cholesterol transport to levels observed in non-diseased rats by decreasing inflammation that impairs cholesterol transport in the disease models.

Tofacitinib was also demonstrated to increase graft survival in rodents and monkeys.

All metabolites of tofacitinib have or are predicted to have ≤ 10-fold potency of tofacitinib for JAK1/3 inhibition.

Secondary pharmacodynamic studies

Inhibition of JAK2 signalling pathway was demonstrated to be responsible for hematological changes (decrease of 33% in reticulocytes counts after a 2-day treatment with 5 mg/kg po corresponding to approximately 6-fold human exposure) in EPO treated monkeys.

Tofacitinib showed off-target inhibition for VEGFR1, MT3, Cam kinase 2α and LynA kinase with IC50s of 3.7, 5.3, 12 and 2.3 µM respectively.

Safety pharmacology programme

Tofacitinib induced a slight inhibition hERG current but had no effect on dog Purkinje fibers and guinea pig right atria. It showed a non-specific myorelaxant effect on isolated rat aorta with an IC_{50} of 3 µM. *In vivo*, it induced an increase in blood pressure and heart rate and a decrease in body temperature in rats at an exposure corresponding to an approximately 62-fold human C_{max} and a transient increase in heart rate in monkeys at an exposure corresponding to a 60--fold human C_{max}. No changes in ECG were observed.

In mice, tofacitinib induced a decrease in locomotor activity at an exposure corresponding to approximately 90-fold human C_{max} and death, seizures, decreased respiration, loss of reflexes at an exposure corresponding to approximately 280-fold human C_{max}. No pro- and anti-convulsivant effect was demonstrated.

Tofacitinib inhibited gastric emptying in rats and increased potassium excretion and in a lesser extend decreased chloride excretion and urine volume.

Pharmacodynamic drug interactions

No animal studies were performed to predict human drug-drug interactions in the absence of an understanding of animal to human homogeny. Prediction of human drug-drug interaction potential was based on in-vitro and in-vivo human data.

2.3.3. Pharmacokinetics

Absorption

Pharmacokinetic parameters were determined in rat, rabbit, dog and monkeys after a single administration.

After IV administration, plasma clearance was high (29 to 62 mL/min/kg in rats, 19.4 mL/min/kg in dogs and 18.2 mL/min/kg in monkeys) and distribution volume was moderate (1.4 to 2.6 L/kg in rats, 1.8 L/kg in dog and 1.7 L/kg in monkeys).

After oral administration, absorption was rapid as indicated by Tmax (around 0.5 h in rats and dogs, 0.9 h in rabbits and 1.5 h in monkeys). Oral bioavailability was moderate in male rats (43.3%), dogs (43%) and monkeys (48%) but was > 100% in female rats.

Elimination half-lives were was 0.6 to 2.8 hours in rats, 1.2 h in dogs, 2.4 h in rabbits and 1.4 to 8.9 h in monkeys.

After repeated administration, in rats and monkeys, systemic exposures increased with the dose and there was no accumulation over time.

In rats, C_{max} and AUC in females were 2 to 3-fold higher than in males. This difference between males and females was less apparent at high doses. There were no marked gender-related differences in monkeys.

Distribution

Tofacitinib was widely distributed in the rat. Maximum concentration was rapid reached in the majority of tissues (0.5 -1 h). Tofacitinib distribution in the brain was limited. After 3 days, tofacitinib was still detected in intervertebral discs, liver, blood vessel walls, kidneys, and ocular tissues containing melanin. After 21 days, measurable concentrations were found in blood vessel walls and ocular tissues containing melanin.

Tofacitinib plasma protein binding was moderate in mouse, dog, monkey and human with unbound fraction of 67%, 80%, 65% and 61% respectively. In the rat, the unbound fraction was concentration-dependant, a composite value of 85% was determined.

Tofacitinib does not bind to α1-acid glycoprotein but moderately binds to human serum albumin. The distribution between red blood cell and plasma compartments seems to be equal.

Metabolism

In vivo, metabolism was studied in rats, monkeys, mice, rabbits and human. Unchanged tofacitinib was the major circulating component. All human metabolites were found in monkeys. In rats, gender differences were noted, M13 was present only in males.

The primary metabolic pathways were due to oxidation of the pyrrolopyrimidine ring (M9), oxidation of the piperidine ring (M6 and M18), *N*-demethylation (M1), oxidation of the piperidine ring side chain (M2), and glucuronidation (M20).

Oxidation seems to be primarily mediated by cytochromes P450, especially CYP3A4 and CYP2C19.

Excretion

Excretion was rapid in every tested species with most of the radioactivity excreted in the first 24 – 48h. The major route of excretion was via the urine in rabbit (51%), monkeys (~ 50%) and human (80%) while it was via feces in the mouse (~60%). In the rat, the excretion was approximately equal through urine and feces.

In bile-cannulated monkeys, the biliary excretion accounted for 25% of the dose.

Tofacitinib was excreted into rat milk where the concentrations were 2-fold higher than serum concentrations. This information has been included in the SmPC section 4.6.

Drug-drug interactions

In vitro, tofacitinib seems to be mainly metabolised by CYP3A4. However, in vivo, part of this enzyme is lesser than expected considering the moderate tofacitinib AUC increase (approximately 2-fold) observed in the DDI study performed with ketoconazole a strong CYP3A4 inhibitor (see Clinical assessment).

According to the European Guidelines on DDI studies, a risk of interaction with substrates of the studied CYPs is unlikely. The calculation of the $[I]/IC_{50}$ ratio (with IC_{50} = 30 µM), with [I] equal to the steady state unbound C_{max}, is <0.02. Likewise, using the total C_{max} obtained with the maximal 10 mg BID dose, i.e. approximately 116 ng/ml or 0.37 µM, the [I]/IC50 is < 0.1.

A clinically relevant interaction with CYP3A4 substrates due to tofacitinib a CYP3A4-inducing effect of toafacitinib is low. This is supported by results observed following the clinical study performed with midazolam, a CYP3A4 probe substrate, which does not show any significant effect of tofacitinib on midazolam pharmacokinetics.

Tofacitinib is not expected to induce CYP2B6.

The risk of tofacitinib interaction related to UGT inhibition is considered to be low.

Tofacitinib is a P-gp and a BCRP substrate. Considering the low permeability of tofacitinib, significant PK changes in case of combination with P-gp inhibitors are expected. A clinical study performed with ketoconazole, inhibiting both CYP3A4 and P-gp, showed about a 2-fold increase in tofacitinib AUC. The quantitative part of each mechanism is unknown. However, another clinical study with cyclosporine (a strong P-gp inhibitor) also shows a significant increase of tofacitinib AUC, about 1.7-fold. These results are in line with *in vitro* data.

Tofacitinib inhibited P-gp efflux transporter but at concentration much higher than the clinical intestinal and systemic concentrations and the calculation of the ratio I/IC50 makes the risk of clinically relevant interaction low.

Based on *in vitro* data, tofacitinib is neither a substrate for BCRP, OCT1 and OCT2 hOATP1B1/1B3 nor an inhibitor of OCT2 and OATP1B1/1B3 at therapeutic concentrations. Therefore, clinical studies with substrate of these transporters are not required. These results are supported by clinical data; tofacitinib does not significantly interact with:

- methotrexate, a known substrate for BCR, OAT1/2/3, OATP1/B1/1B3, MDR1,
- metformin, a known substrate for OCT1/2/3 and MATE,
- atorvastatin that is a substrate and an inhibitor for OATP.
-

Therefore, the risk of tofacitinib interaction related to transporters for instance BCRP, OCTs, OATs, and OATPs is low.

The effect of tofacitinib as a substrate on renal secretory transporters like OCT1 and OATs has not been investigated.

The effect of tofacitinib as a substrate and inhibitor of BSEP has not been studied.

2.3.4. Toxicology

Single dose toxicity

When administered orally as a single dose, tofacitinib induced mortality in rats at doses ≥ 500 mg/kg. In monkeys, oral doses up to 1000 mg/kg/day were not lethal.

Repeat dose toxicity

In the 6-week and 6-month rodent studies, Sprague-Dawley rats were administered oral doses of tofacitinib at up to 100 mg/kg/day. In both studies, effects were consistent with the inhibition of JAK1/3 (slight decreases in circulating lymphocytes and lymphoid depletion in spleen, thymus, mesenteric lymph node, and

the bone marrow) and with other effects consistent with JAK2 inhibition (decreases in RBC parameters and reticulocytes). The observed effects were dose- and time dependent and were generally reversed in the 4-week recovery group from the 6-week study. Additionally in the 6-month study, tofacitinib-related increase in severity and incidence of alveolar histiocytosis and lung interstitial inflammation was observed in males at ≥10 mg/kg/day and females at ≥100 mg/kg/day. Similar findings were observed in the 2-year rat carcinogenicity study and consisted of alveolar macrophage infiltrates and alveolar proteinosis at ≥30 mg/kg/day and females at ≥10 mg/kg/day.

In the 4-week toxicity study cynomolgus monkeys at ≥10 mg/kg/day there were decreases in lymphocytes, lymphocyte subsets, natural killer (NK) cells, and hemoglobin. The recovery of CD16+ and CD3- cells was not observed in 2/4 animals at 50mg/kg at the end of the recovery period. Reversibility of treatment was not evaluated in the 39 week study. Treatment-related findings at ≥50 mg/kg/day consisted of death, decreased activity, decreased RBC parameters, and granulocytic depletion in the bone marrow, active bacterial and/or viral infections which were attributed to immunosuppression, increases in ALT and AST and decreases in serum calcium. The effects increased in severity with dose but were generally reversed in the recovery group. In the 39-week monkey study, decreases in lymphocytes, lymphocyte subsets, and NK cells occurred at all doses, whereas the effects on RBC parameters occurred at ≥2 mg/kg/day. In both studies, the effects on lymphocytes, lymphocyte subsets, and the immune system, were considered to be consistent with the intended JAK1/3 pharmacological activity and decreases in RBC parameters were consistent with JAK2 inhibition.

Lymphomas occurred in the 39-week monkey study. Two of the 3 lymphomas were B cell lymphomas and positive for LCV by immunohistochemical (EBNA-2) and in situ hybridization (EBER-1) staining. One of the 3 monkeys had a lymphoma in the peri-thymic fat that was stated to be a T cell lymphoma based on immunohistochemical staining. This lymphoma was not stained for EBER-1 or EBNA-2. There is evidence that immunosuppressive therapy results in decreased numbers of LCV-specific cytotoxic T lymphocytes which are therefore unable to control the growth of EBV-transformed B cells. For the 39-week monkey study, all of the monkeys were found to be infected with LCV based on the presence of anti-LCV antibodies in pre-study serum samples. Therefore, the LCV-associated lymphomas observed in the 39-week monkey study were attributed to be secondary to immunosuppression.

The occurrence of lymphomas was not reported in the study using juvenile cynomolgus monkeys using the same dose levels, dosing regimen and of the same duration. The mechanism for the lymphocytic hyperplasia in the adult study is stated to be unknown. In this study the unbound AUC in the monkeys at the NOAEL was approximately half of the unbound AUC for the 10mg BID dose and similar to the unbound AUC of the 5mg BID human dose.

Immunophenotyping of lymphocyte subsets in peripheral blood in the 6-month rat and 4- and 39-week monkey studies revealed decreases in circulating total T cells, CD4 (helper) and CD8 (cytotoxic) T cells and NK cells at ≥1 mg/kg/day in rats, and ≥0.5 mg/kg/day in monkeys. Decreases in B cells were observed in rats (≥1 mg/kg/day), but not in monkeys.

Other findings related to administration of tofacitinib included effects on the hepatic and gastrointestinal systems. Emesis in monkeys occurred at doses ≥50 mg/kg/day. In studies of up to 14 days duration in rats and monkeys, gastrointestinal effects occurred at doses ≥300 and ≥200 mg/kg/day, respectively. Dilatation and red foci of the stomach and dilatation of the intestine occurred in monkeys at ≥200 mg/kg/day. Decreased gastric motility resulting in enlarged stomachs and multifocal slight to moderate necrosis of the glandular stomach occurred in rats at doses ≥1000 mg/kg/day. This is also consistent with the decreased intestinal motility observed in the safety pharmacology study in rats. In the 39 week repeated dose toxicity

study in the cynomolgus monkey, there were reports of ulceration /erosions in the stomach, associated with infiltrative lymphoma which resulted in haemorrhage into the upper gastrointestinal tract in one female at 10mg/kg/day. Also loose, mucoid stools with blood-like substance were reported at 10, 50 and 100mg/kg/day in the one-month repeated dose toxicity study in the cynomolgus monkey.

The effects on serum transaminases were mild in rats and monkeys and were generally observed at high exposures in acute or short-term (≤6-week duration) studies. At the LOEL of 10 mg/kg/day in the 6-week rat and 4-week monkey studies, there were slight transaminase increases (with no histopathological correlate). No hepatocellular effects were observed in the 39-week monkey study at the highest dose tested (10 mg/kg/day). In the 6-month rat study, there was an increase in liver weight accompanied by hepatocellular hypertrophy at the high dose (100 mg/kg/day) with no evidence of hepatocellular degeneration or necrosis, and no treatment-related changes in serum transaminases.

Genotoxicity

Tofacitinib was assessed in a series of genetic toxicology assays consisting of the microbial reverse mutation, in vitro mammalian cell assay, in vitro cytogenetics (human lymphocyte), a rat UDS study, and in vivo rat micronucleus assay.

The Ames test was negative. In the chromosome aberration test, increases of abnormal cells in presence of metabolic activation up to 14% were observed at doses ≥1700 µg/mL inducing ≥ 48% of mitotic index. Furthermore, an increase of polyploidy was observed in absence of metabolic activation (up to 3.5%)

Other than a positive response in the in vitro cytogenetic study at high (cytotoxic) concentrations, tofacitinib was negative in the battery of genotoxicity studies.

Carcinogenicity

A 6-month carcinogenicity study in CB6F1/Jic-Tg(rasH2) mice was selected to supplement the 2-year carcinogenicity study in rats. No evidence of treatment-related carcinogenicity was observed in the 6-month rasH2 transgenic mouse study at exposures up to 38 times the clinical exposure level. In the 2-year rat carcinogenicity study the top dose was lowered from 100 to 75 mg/kg/day during month 4 of the study because of the early deaths in high dose females that were due to infection (Tyzzer's Disease). Fewer than 50% of the animals survived to the planned study termination at 2 years in all groups including the control groups. However, there were a sufficient number of animals exposed to the test compound for a sufficient duration of time to evaluate carcinogenic potential.

Treatment-related neoplastic findings included: benign Leydig cell tumors in males at ≥30 mg/kg/day; benign angiomas in the mesenteric lymph nodes in males at 10 mg/kg/day; benign thymomas in thymus in females at 100/75 mg/kg/day; and malignant hibernomas in females at ≥30 mg/kg/day.

The Leydig cell tumors observed in the rat carcinogenicity study were attributed to JAK2 inhibition of PRL signaling within the Leydig cells resulting in the same intracellular environment that is caused by dopamine agonists (DAs), which decrease circulating levels of PRL. An investigative in vitro study conducted to corroborate this premise demonstrated that tofacitinib can completely block JAK2–mediated PRL signaling in Leydig cells, supporting a probable mechanism for induction of Leydig cell tumors similar to that of DAs. However, there was no in vivo corroborative study, for example there was no measurement of serum PRL, testosterone or LH levels. The applicant's explanation is plausible.

Increased malignant hibernoma (malignancy of brown adipose tissue) incidence in female rats was associated at exposures greater than or equal to 83 times the clinical exposure level.

There was a slight increase in the incidence of benign angiomas only in low-dose male rats, which was statistically significant in a pairwise comparison. There was no dose-response, with lack of statistical significance in the trend test and the increased incidence of angiomas occurred only in a single species, only in a single sex, and only at a single dose level. There was no other evidence of test article-related vascular endothelial neoplasia in the rat carcinogenicity study. All of the angiomas in treated males occurred within mesenteric lymph nodes. The data do not support a relationship of angiomas to treatment.

An increased incidence of benign thymomas occurred only in high-dose female rats. Thymomas have been observed previously in rat carcinogenicity studies of other immunosuppressive drugs. Based on the high exposure multiples for occurrence of thymoma (187 times the clinical exposure level), and the precedence for this finding with other immunosuppresive drugs these benign tumors are not considered a significant risk to humans at therapeutic exposures.

Reproduction Toxicity

Tofacitinib was teratogenic (visceral and skeletal abnormalities) in rats (in presence of maternal toxicity) and rabbits (in absence of maternal toxicity) at doses of ≥100 mg/kg/day and ≥30 mg/kg/day, respectively corresponding to 58- and 2.9- times the clinical exposure level (total AUC24 in humans at a dose 5 mg twice daily). This has been reflected in section 4.6 and 5.3 of the SmPC.

Tofacitinib had no effects on male fertility, sperm motility and concentration at the high dose of 100 mg/kg/day. Treatment-related effects on female reproduction were decreased pregnancy rate, decreases in the numbers of corpora lutea, implantation sites, and viable fetuses, and an increase in early resorptions at the 100 mg/kg/day dose. In the peri/post-natal development study in rats, the number of delivered pups and the number of live born pups were reduced, as well as a reduction in pup survival at the 50 mg/kg/day dose (see SmPC sections 4.6 and 5.3). No effect occurred on sexual maturation or the ability of the F1 generation rats to learn, mate, and produce viable F2 generation fetuses.

In the juvenile rat fertility study, there was no evidence of developmental toxicity (sexual landmarks) or reproductive toxicity (mating and fertility) following the juvenile treatment period. A 1-month study in juvenile rats showed test article-related effects on immune and hematology parameters at all doses, which were consistent with JAK1/3 and JAK2 inhibition, and were reversible.

Toxicokinetic data

Table 7 - Exposure margins based on AUC and Cmax

Type of study	Species	Duration	NOAEL (mg/kg/day)	AUC unbound[a] (ng.h/mL) at NOAEL[a]	Cmax unbound[a] (ng/mL) at NOAEL[a]	Exposure margin[b] based on	
						AUC	Cmax
Repeat-dose toxicity	Rat	6 months	< 1 (M)	217	96	**0.7**	**2.7**
			< 1 (F)	604	324	**2.0**	**9**
	Monkey	39 weeks	< 0.5	25.6	12.9	**0.16**	**0.4**
Carcinogenicity	Rat	2 years	< 10 (M)	3298	1360	**10.6**	**38.8**
			10 (F)	6672	2414	**21.5**	**68**
	Mouse	6 months	200	11591	3672	**37.4**	**104**

Reprotoxicity	**Rat**	Fertility	100 (M)	-	4182	**-**	**119**
			1 (F)	-	222	**-**	**6.3**
	Rat	Segment II	30	24990	5406	**80.8**	**154**
	Rabbit	Segment II	10	1470 (Total)	610 (Total)	**2.8**	**10**

[a] AUC and Cmax on the last time point. Gender and time point of determination are only specified if the difference was considered relevant. Otherwise, average values are given.
Unbound exposure values based on unbound fractions for the represented species: Rat = 0.85, Monkey = 0.65, Mouse = 0.67

[b] Unbound exposure margin calculated based on total human AUC(0-24) of 507 ng.h/mL and Cmax of 58 ng/mL converted to unbound fraction (fu = 0.61) of **309 ng.h/mL** and **35 ng/mL** respectively at a dose of 5 mg BID.

Local Tolerance

Tofacitinib was negative for contact sensitization in a local lymph node assay (LLNA) and was not considered an ocular or primary skin irritant in rabbits. There was no evidence of hemolysis observed in an in vitro hemolysis compatibility study conducted with an IV formulation of tofacitinib. There was no evidence that tofacitinib was phototoxic in the 3T3-Neutral Red Uptake (NRU) assay or in the in vivo phototoxicity study in pigmented rats

Other toxicity studies

Seven impurities were specified in the drug substance. During the first MAA the only other concerns that remained unsolved were related to qualification of drug substance impurities specified above 0.15% according to ICH Q3A: a structure-based assessment with the in silico tool was lacking for impurity CP-703058 and since the impurity PF 05198213 was not present in the batches used in the genotoxicity studies but only in the batch used in the 39-week juvenile monkey study, a thorough genotoxic characterisation based on bacterial mutagenicity assay according to ICH M7, was asked.

Following the assessment of the in silico reports for mutagenicity risks based on structure (DEREK and SARAH Nexus using ICH M7 settings), CP-703058 is considered to be non-mutagenic.

As regards the potential genotoxicity of impurity PF-051 98213, a thorough re-evaluation of this issue, mainly focused on the nitrile moiety, electrophilicity and other physic-chemical considerations, revealed that the impurity was negative in two complementary in silico (DREK and SARAH) systems and that the QSAR predictions were reliable.

2.3.5. Ecotoxicity/environmental risk assessment

The results of the study conducted according to OECD 209 (260E-249) were considered contradictory and inadequate to derive a NOEC. Abnormal promotion of the respiration rates could be observed in laboratory batches for both the test substance as well as the reference substance.

The Applicant has conducted a new study with tofacitinib free base, with an updated ERA.

The applicant has submitted the final study report (Project No. 260E-297 Study No. CP-690550) of an Activated Sludge, Respiration Inhibition Test (OECD Guideline 209) on tofacitinib free base, which was conducted in compliance with GLP. The test contained control, reference and treatment groups. The control replicates were used to determine the background respiration rate of the sludge and were not dosed with the test or reference substance. The reference group was dosed with 3,5-dichlorophenol, a known inhibitor of

respiration, at concentrations of 3, 15 and 50 mg/L. The treatment group was dosed with tofacitinib at concentrations of 10, 100, and 1000 mg/L. The 1000 mg/L treatment was tested in triplicate. An abiotic control was dosed with the test substance at a concentration of 1000 mg/L to differentiate between abiotic oxygen uptake by the test substance and microbial respiration. After an exposure period of three hours, the respiration rates of the test solutions were measured using a YSI Model 5000 Dissolved Oxygen Meter.

An inhibitory dose response effect was not observed for the treatment groups. The EC50 value for tofacitinib is greater than 1000 mg/L, the highest concentration tested. The EC10 value for tofacitinib is >1000 mg/L, the highest concentration tested. The abiotic treatment mixture dosed with 1000 mg/L of tofacitinib had a respiration rate of 0.2 mg O2/L/hr showing there was no significant uptake or release of oxygen resulting from abiotic reactions of the test substance. The results of the test indicate that tofacitinib will not adversely affect aerobic microbial treatment plants.

The updated ERA indicates that tofacitinib will not present an environmental risk following patient use.

Table 8 - Summary of main study results

Substance (INN / Invented Name): Tofacitinib (XELJANZ)			
CAS-number (if available):540737-29-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log D = 0.114 (pH 4) Log D = 1.19 (pH 7) Log D = 1.18 (pH 9)	No Potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Log D = 1.19 (pH 7)	B/not B
	BCF	ND	B/not B
Persistence	DT50 or ready biodegradability	T1/2 = 28.9 h (sludge OECD314B) T1/2 = 26.3 – 52.8 days (aquatic sediment OECD 308)	P/not P
Toxicity	NOEC or CMR	ND	T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.05	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 102 (0.01M CaCl2) 4266 (Clay Loam TB-PF soil) 977 (Sandy soil) 10000 (Silty loam sediment) 4786 (Sandy sediment)	
Ready Biodegradability Test	OECD 301		
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =	Not required if readily biodegradable
Phase IIa Effect studies			

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	11	mg/L	Species Pseudokirchinella subcapitata
Reproduction Test	OECD 211	NOEC	4.8	mg/L	*Daphnia* sp.
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	2.9	mg/L	Species Pimephales promelas
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50 NOEC (EC10)	>1000 1000	mg/L mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	ND	L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	ND		for all 4 soils
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	%effect	ND	mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	ND	mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	ND	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	ND	mg/kg	
Sediment dwelling organism		NOEC	46	mg/kg	Species Chironomus riparius

2.3.6. Discussion on non-clinical aspects

Tofacitinib is a selective inhibitor of Janus kinases with a high affinity for JAK1 and 3 and for JAK2 in a lesser extent. Inhibition of JAK1/3 prevents inflammation signalling pathway as demonstrated by decreased plasma cytokines (IL-6 and IL-17) in rodent arthritis models. The inhibition of JAK2 signalling pathway seems to be responsible for haematological effects (decrease of RBC parameters and reticulocytes). In mouse and rat arthritis model, tofacinitib showed an effect on the decrease of inflammatory endpoints (decrease of cytokine levels in plasma and arthritic tissue) and on bone resorption but it had no effect on cartilage destruction which is a key endpoint in rheumatoid arthritis.

In safety pharmacology studies, tofacitinib induced an increase in blood pressure and heart rate and a decrease in body temperature in rats at an exposure corresponding to a 62-fold human Cmax and a transient increase in heart rate in monkeys at an exposure corresponding to a 61-fold human Cmax. It should be noted that increased blood pressure was also observed in patients treated with tofacitinib.

In mice, tofacitinib induced a decrease in locomotor activity at an exposure corresponding to 45-fold human Cmax and death, seizures, decreased respiration, loss of reflexes at an exposure corresponding to 140-fold human Cmax. No pro- and anti-convulsivant effect was demonstrated.

Tofacitinib inhibited gastric emptying in rats and increased potassium excretion and in a lesser extend decreased chloride excretion and urine volume.

Pharmacokinetic and toxicokinetic studies were conducted in mice, rats, rabbits, dogs and monkeys in order to investigate absorption, plasma kinetics, distribution, metabolism and excretion of tofacitinib. Most of these studies were conducted using the oral route, some of them using the IV route.

After oral administration, absorption was rapid, bioavailability was moderate and elimination half-life was short. After repeated administration, there was no accumulation. Exposure in female rats was 2 to 3-fold higher than in male rats. There was no gender-related difference in other species. Distribution was wide. Plasma protein binding was moderate.

The primary metabolic pathways were due to oxidation of the pyrrolopyrimidine ring, oxidation of the piperidine ring, N-demethylation, oxidation of the piperidine ring side chain, and glucuronidation. Oxidation seems to be primarily mediated by cytochromes P450, especially CYP3A4 and CYP2C19.

Excretion was rapid in every tested species. The major route of excretion was via the urine in rabbit, monkeys and human while it was via feces in the mouse. In the rat, the excretion was approximately equal between urine and feces.

According to the European Guidelines on DDI studies, a risk of interaction with substrates of the studied CYPs is unlikely this is in line with results obtained.

Based on *in vitro* data, tofacitinib is neither a substrate for BCRP, OCT1 and OCT2 hOATP1B1/1B3 nor an inhibitor OCT2 and OATP1B1/1B3 at therapeutic concentrations. Therefore, clinical studies with substrate of these transporters are not required. These results are supported by clinical data, tofacitinib does not significantly interact with:

- methotrexate , a known substrate for BCR, OAT1/2/3, OATP1/B1/1B3, MDR1
- metformin , a known substrate for OCT1/2/3 and MATE,
- atorvastatin that is a substrate and an inhibitor for OATP.
-

Therefore, the risk of tofacitinib interaction related to transporters for instance BCRP, OCTs, OATs, and OATPs is low.

Regarding induction of CYP2B and 2C, the lack of *in vitro* studies on the inductive effect of tofacitinib on CYP2B and 2C has been discussed. However, considering the complexity of the mechanisms behind induction, the Applicant's response was considered insufficient to adequately rule out a risk of induction for CYP2B6. Thus, the Applicant has performed an *in vitro* study with human cryopreserved hepatocytes assessing the inducing effect of tofacitinib on CYP2B. As regard to the results, at therapeutic concentrations and also at concentration equal to 50 × unbound Cmax at steady-state, tofacitinib is not expected to induce CYP2B6. Therefore, clinical risk of CYP2B6 induction by tofacitinib is low.

The effect of tofacitinib as a substrate and inhibitor of BSEP has not been studied however knowing the weak part of biliary secretion in tofacitinib elimination (approximately 14%) this issue is not considered relevant.

Tofacinitib was administered up to 6 months in rats and up to 39 weeks in monkeys. The treatment-related effects were consistent in both species.

The main organs affected were the haemapoietic and immune system. There was a partially reversible decrease in white blood cells leading to immunodepression and potentially lethal infections. This effect on immunity was also seen in humans with an increased incidence of infections during clinical trials.

A decrease in red blood cells and reticulocytes was also evident in animals. Effects on the liver, on the gastrointestinal tract (necrosis, erosion, dilation, hemorrhage) and the lung (interstitial inflammation) were observed. In the 39 week repeated dose toxicity study in the cynomolgus monkey, there were reports of ulceration /erosions in the stomach, associated with infiltrative lymphoma which resulted in haemorrhage into the upper gastrointestinal tract in one female at 10mg/kg/day. Also loose, mucoid stools with blood-like

substance were reported at 10, 50 and 100mg/kg/day in the one-month repeated dose toxicity study in the cynomolgus monkey. The aetiology for the observed stool changes observed in the monkey 1–month toxicity study was related to secondary infections, which were related to high doses that exceeded the MTD and lead to excessive immunosuppression.

In the 39-week study in monkeys, three animals treated with the high dose of 10 mg/kg corresponding to 1.5 times the human exposure developed lymphoma: two B-cell lymphomas associated with lymphocryptovirus and one T-cell lymphoma. However, the lymphocyte hyperplasia also observed in this study was not associated with LCV.

No NOAEL could be defined. The LOAEL were 1 mg/kg in rats and 0.5 mg/kg in monkeys representing safety margins of 0.4 and 1 in male and female rats and 0.04 in monkeys based on AUC.

Tofacitinib underwent a complete genotoxicity tests battery. The Ames test was negative. In the chromosome aberration test, increases of abnormal cells in presence of metabolic activation were observed. Furthermore, an increase of polyploidy was observed in absence of metabolic activation. Nevertheless, this effect is not considered relevant to humans. In summary, tofacitinib is not considered as a genotoxic component at therapeutic concentrations.

Tofacinitib was not carcinogenic in a 6-month study in transgenic TgrasH2 mice at systemic exposure levels in the mice of 38 times the clinical exposure.

In the rat carcinogenicity study there was an increased incidence of hibernomas, angiomas, thymomas and pancreatic tumors. The Applicant has provided historical controls data of Covance and of RITA databases, which are contemporary of the period of the 2-year rat carcinogenicity study of tofacitinib.

When combined with a 2-year rat carcinogenicity study, a 6-month carcinogenicity study in TgrasH2 mice is an appropriate alternative to a conventional 2-year mouse bioassay for carcinogen hazard identification.

There was an increased malignant hibernoma incidence in female rats at systemic exposures ≥83 times the clinical exposure levels. There may be different pathological processes in the rat and human which could decrease the likelihood that the hibernomas in female rats are relevant to humans. Tofacitinib is not considered genotoxic and the increased incidence of hibernomas in female rats may be due to a pharmacological proliferative effect on BAT. Overall, hibernomas observed in female rats treated with tofacitinib are not considered a significant risk for human safety at clinical exposures. This is based on a non-genotoxic proliferative effect with an adequate safety margin. Additionally, the differences in hibernoma incidence, malignancy potential, and location between rats and humans, and the association of tofacitinib with hibernoma in only a single rodent species and sex, decrease the likelihood that the hibernomas in rats are relevant to humans.

An increased incidence of thymomas occurred only in high-dose female rats (systemic exposures 187 times clinical exposure). Thymomas have been observed previously in rat carcinogenicity studies of other immunosuppressive drugs. Based on the high exposure multiples for occurrence of thymoma, and the precedence for this finding with other immunosuppresive drugs these benign tumors are not considered a significant risk to humans at therapeutic exposures.

There was a slight increase in the incidence of benign angiomas only in low-dose male rats, which was statistically significant in a pairwise comparison. There was no dose-response, with lack of statistical significance in the trend test and the increased incidence of angiomas occurred only in a single species, only in a single sex, and only at a single dose level. There was no other evidence of test article-related vascular endothelial neoplasia in the rat carcinogenicity study. All of the angiomas in treated males occurred within mesenteric lymph nodes. The data do not support a relationship of angiomas to treatment.

Finally, the incidence of the pancreatic islet tumors observed in the 2-year rat carcinogenicity study of tofacitinib falls within the range of the incidence of this type of tumors reported in Covance and RITA databases

The occurrence of lymphomas was reported in the 39 week repeated dose toxicity study in adult cynomolgus monkeys but not in the study using juvenile animals using the same dose levels, dosing regimen and of the same duration. The differences between adult and juvenile monkeys regarding the lymphomas observed in adult and not in juvenile monkeys could not be explained. The fact that lymphoproliferative effects and lymphoma have been observed in patients treated with tofacitinib is included in the risk management plan (RMP).

Tofacitinib had no effect on male rat fertility but decreased female fertility. It was teratogenic in rats and rabbits. In the pre- and postnatal development study, it induced a decrease in F1 pups survival.

As regards the potential genotoxicity of impurity PF-051 98213, a thorough re-evaluation of this issue revealed that the impurity was negative in two complementary in systems and that the QSAR predictions were reliable. Consequently no additional in vitro data is considered necessary; thus no additional in vitro mutagenicity evaluation of PF-05198213 is considered necessary, consistent with ICH M7 principles.

Based on the definitive genotoxicity assessment indicating no concerns for the different impurities, the currently proposed impurities specification limits although wide, are considered adequate since they allow flexibility in the Quality by Design manufacturing process, ensure patient safety and avoid unnecessary batch failure when operating with the approved process ranges.

The results of the ERA study conducted according to OECD 209 (260E-249) are contradictory and inadequate to derive a NOEC. An updated ERA was submitted and indicates that tofacitinib will not present an environmental risk following patient use.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considered that the non-clinical data submitted is acceptable to support this application.

2.4. Clinical aspects

2.4.1. Introduction

This Marketing Authorisation Application (MAA) concerns tofacitinib citrate (CP-690,550), a synthetic, small molecule inhibitor of the Janus kinase (JAK) family of kinases, for the treatment of rheumatoid arthritis. The product, presented as 5 mg film-coated tablets for oral administration, was proposed at the time of the application for the treatment of moderate to severe, active rheumatoid arthritis in adult patients who have responded inadequately to or are intolerant of methotrexate. CHMP considered that this could also be understood as patients who have received one or more DMARDs given that methotrexate is viewed as first line anchor treatment for rheumatoid arthritis. It is therefore implicit that patients who are MTX inadequately responsive or intolerant would include patients who may have received other DMARDs, including other conventional synthetic DMARDs or biological DMARDs. Tofacitinib is recommended to be given in combination with methotrexate unless patients are intolerant of methotrexate or when methotrexate is inappropriate, in which case tofacitinib is recommended as monotherapy.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study/Duration/ Background DMARD Treatment/ Prior DMARDs	Study Treatment Advancement Scheme	Treatment Groups[c]	Number of Subjects[a]
Phase 3 Studies			
A3921032 [36] ORAL STEP[d] 6 months Background MTX TNFi-IR	All placebo advanced to tofacitinib at Month 3.	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo → tofacitinib 5 mg BID Placebo → tofacitinib 10 mg BID	133 134 66 66
A3921044 [39] ORAL SCAN[d] 24 months Background MTX MTX-IR	Placebo IR advanced to tofacitinib at Month 3; all remaining placebo advanced to tofacitinib at Month 6.	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo → tofacitinib 5 mg BID Placebo → tofacitinib 10 mg BID	321 319 81 79
A3921045 [37] ORAL SOLO[d] 6 Months None[e] (monotherapy study) DMARD-IR	All placebo advanced to tofacitinib at Month 3.	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo → tofacitinib 5 mg BID Placebo → tofacitinib 10 mg BID	244 245 61 61
A3921046 [38] ORAL SYNC[d] 12 Months Background csDMARD DMARD-IR	Placebo IR advanced to tofacitinib at Month 3; all remaining placebo advanced to tofacitinib at Month 6.	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo → tofacitinib 5 mg BID Placebo → tofacitinib 10 mg BID	318 318 79 80
A3921064 [35] ORAL STANDARD[d] 12 Months Background MTX MTX-IR	Placebo IR advanced to tofacitinib at Month 3; all remaining placebo advanced to tofacitinib at Month 6.	Tofacitinib 5 mg BID Tofacitinib 10 mg BID Placebo → tofacitinib 5 mg BID Placebo → tofacitinib 10 mg BID Adalimumab 40 mg SC QOW	204 201 56 52 204
A3921069 [3] ORAL START[d] 24 months None[e] (monotherapy study) MTX-naïve	No treatment advancement	Tofacitinib 5 mg BID Tofacitinib 10 mg BID MTX titrated to 20 mg/week	374 398 186
Phase 2 Studies			
A3921019 [41] 6 weeks None (monotherapy study) MTX-IR or TNFi-IR	No treatment advancement	Tofacitinib: 5 mg BID 15 mg BID 30 mg BID Placebo	 61 69 69 65
A3921025 [42] 6 months Background MTX MTX-IR	IR on placebo or tofacitinib 1 mg BID, 3 mg BID, or 20 mg QD advanced to tofacitinib 5 mg BID at Month 3.	Tofacitinib: 1 mg BID 3 mg BID 5 mg BID 10 mg BID 15 mg BID 20 mg QD Placebo	 71 68 71 75 75 80 69

A3921035 [40] 6 months None (monotherapy study) DMARD-IR	IR on placebo or tofacitinib 1 or 3 mg BID advanced to tofacitinib 5 mg BID at Month 3. Adalimumab advanced to tofacitinib 5 mg BID at Month 3.	Tofacitinib: 1 mg BID 3 mg BID 5 mg BID 10 mg BID 15 mg BID Adalimumab 40 mg SC QOW for 10 weeks Placebo	 54 52 50 61 57 53 59
A3921039 [43] 3 months Background MTX MTX-IR	No treatment advancement	Tofacitinib: 1 mg BID 3 mg BID 5 mg BID 10 mg BID Placebo	 28 28 28 28 28
A3921040 3 months None (monotherapy study) DMARD-IR	No treatment advancement	Tofacitinib: 1 mg BID 3 mg BID 5 mg BID 10 mg BID 15 mg BID Placebo	 53 53 52 53 54 53
A3921068 12 months None MTX-naïve	No treatment advancement	Tofacitinib 10 mg BID plus MTX titrated to 20 mg/week Tofacitinib 10 mg BID Placebo plus MTX titrated to 20 mg/week	36 36 37
A3921073 4 weeks Background MTX MTX-IR	No treatment advancement	Tofacitinib: 10 mg BID Placebo	 15 14
Long-term Extension Studies			
A3921024 Ongoing[b]	Dose adjustments allowed as per protocol.	Tofacitinib 5 mg BID Tofacitinib 10 mg BID	1059 3322
A3921041 Completed	Dose adjustments allowed as per protocol.	Tofacitinib 5 mg BID Tofacitinib 10 mg BID	381 105

Source: A3921025 CSR Table 13.1.1, A3921035 CSR Table 13.1.1, A3921039 CSR Table 13.1.1, A3921040 CSR Table 14.1.1.1, A3921032 CSR Table 14.1.1.1, A3921044 Year 1 CSR Table 14.1.1.1.2, A3921045 CSR Table 14.1.1.1, A3921046 CSR Table 14.1.1.1.2, A3921064 CSR Table 14.1.1.1.2, A3921019 CSR Table 13.1.1, A3921068 CSR Table 14.1.1.1, A3921073 CSR Table 14.1.1.1, A3921069 Year 1 CSR Table 14.1.1.1, A3921041 CSR Table 14.1.1.1, A3921024 Interim CSR Table 1.2.1.

BID=twice daily, MTX=methotrexate, DMARD=disease-modifying anti-rheumatic drug, SC=subcutaneous, QOW=every other week, QD=once daily, mg=milligrams, TNFi=tumour necrosis factor inhibitor, IR=inadequate responder, CSR=clinical study report, csDMARD=conventional synthetic DMARD.

a. Number of subjects assigned to study treatment (randomized).

b. Ongoing as of 31 March 2015.

c. → Denotes a separation of one dosing period from the other (advancement).

d. Study name as used in external communications and publications.

e. Antimalarials were allowed.

2.4.2. Pharmacokinetics

The clinical pharmacology of tofacitinib was mainly evaluated in healthy volunteers and no formal PK investigations in RA patients at the claimed dose have been performed. PK data in RA patients are available in some specific studies such as DDI study with methotrexate (A3921013), cholesterol and lipoprotein kinetics (A3921130) and measured GFR (A3921152).

The clinical pharmacology of tofacitinib is derived from 19 in vitro studies; 25 Phase 1 studies comprising 20 clinical pharmacology and 5 biopharmaceutics studies; 1 exploratory Phase 2 study in RA subjects providing synovial pathobiology information; 5 Phase 2 studies, 1 Phase 3 and 1 long-term open-label study in RA

subjects providing population PK information and 5 Phase 2 studies and 2 long term extension studies in RA subjects providing Exposure-Response information.

The analytical methods supporting tofacitinib PK analysis were adequately developed since their validation was compliant with the specifications required. The use of an achiral method is supported since no inter-conversion was recorded in vivo.

The 5 biopharmaceutical studies included in the present application comprise study A3921077 (absolute BA study), A3921005 (relative BA and food effect study), A3921076, (food effect study), A3921075 (pivotal BE study) and A3921135 (BE study in Asian volunteers).

Absorption

Tofacitinib is rapidly (Tmax=0.5-1 h) and efficiently absorbed. Study A3921077 showed that tofacitinib has an absolute BA of 74% after administration of 10 mg oral commercial tablet vs a tofacitinib IV formulation (10 mg, 30-minute IV infusion) with a total clearance after IV administration (CLiv) of approximately 413 mL/min.

Below is a tabulated summary of PK parameters in healthy subjects after single and multiple administrations:

Parameter	N	Geometric Mean	% CV	Median	Percentiles	
					2.5	**97.5**
Single Dose Parameters						
AUC∞ (ng.h/mL/10 mg)*	398	282	28.1	289	159	483
Cmax(ng/mL/10 mg)*	419	83.2	36.4	83.7	40.5	160
Tmax (h)	419	NC	NC	0.500	0.250	4.08
Steady State Parameters						
AUCtau (ng.h/mL/10mg)*	75	311	60.1	307	171	665
Cmax (ng/mL/10 mg)*	75	79.4	42.4	81.3	41.0	159
Tmax (h)	75	NC	NC	1.00	0.250	4.00
Ctrough (ng/mL/10mg)*	74	4.98	111	4.02	1.36	23.5
Rac	51	1.12	55.2	1.15	0.724	2.19
PTR	74	16.7	101	16.1	3.90	71.6
Additional Parameters						
t1/2(h)	472	3.04	24.1	3.10	1.92	4.69
CL/F (L/h)	467	34.9	34.8	34.5	18.1	63.2

Source: PMAR-00210, Appendix 10
N-Number of observations; %CV-Coefficient of variation;NC-Not calculated
*Normalized to 10 mg tofacitinib, under assumption of linearity across doses (dose ranges of 0.1 to 100 mg for single dose and 5 to 50 mg BID for multiple doses)
Rac-Observed accumulation ratio. Defined as AUCtau at steady-state/AUCtau following single dose
PTR-Peak to trough ratio, defined as Cmax at steady-state/Ctrough at steady-state
CL/F-defined as Dose/AUC∞ following single dose administration; Dose/AUCtau at steady-state.

Note: Summary statistics for Ctrough excluded observations where Ctrough <BLQ (N = 2).

All formulations demonstrated bioequivalence in studies A3921075 and A3921135 in terms of rate and extent of absorption.

Administration with food causes a reduction in Cmax, but exposure, considered more important to efficacy, is equivalent in the presence and absence of food. Tofacitinib is recommended to be given with and without food.

Distribution

Following IV dosing, the apparent steady-state volume of distribution (Vss) of tofacitinib was estimated to be 87 L, suggesting distribution into tissues (Study A3921077). The fraction of tofacitinib unbound (fu) to plasma proteins in humans was determined by in vitro methods to be 0.61. Tofacitinib does not bind to α1-acid glycoprotein (fu ~1), but binds moderately to human serum albumin (fu 0.51). The blood-to-plasma concentration ratio for tofacitinib determined in vitro at 1 μM (312 ng/mL) was 1.2, indicating relatively equal distribution of drug between the red blood cell and plasma. The total clearance after IV administration (CLiv) is approximately 413 mL/min.

Elimination

In vitro and in vivo studies indicate that tofacitinib is extensively metabolized although more than 65% of the total circulating radioactivity in the human mass balance study (A3921010) was accounted for by unchanged tofacitinib. The remaining radioactivity in plasma was attributable to 8 metabolites, each accounting for <8% of the total radioactivity.

The major metabolic pathways involve oxidation of the pyrrolopyrimidine ring, oxidation of the piperidine ring, piperidine-ring side-chain oxidation, and conjugation with glucuronic acid.

Of the principal metabolites, the most potent is M2 with an IC50 at JAK1 of ~81nM (cf 3.2nM for tofacitinib) and 216 nM at JAK3 (cf 1.6 nM for tofacitinib). M1 has IC50 values of >10,000 and 8120 nM at JAK1 and JAK3 respectively. The unresolved metabolites in plasma only constitute a small proportion of the radioactivity (<10%) in the mass balance studies.

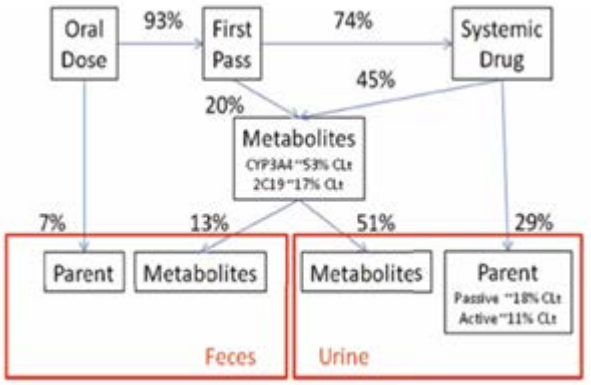
The role of CYP450 enzymes involved in the metabolism of tofacitinib was investigated in incubations with human liver microsomes in the absence and presence of specific chemical inhibitors of individual human CYP450s and with recombinant CYPs.

In the presence of a potent CYP3A inhibitor, ketoconazole, formation of oxidative metabolites was significantly (>70%) inhibited; while inhibitors of CYP2D6 (quinidine), CYP2C9 (sulfaphenazole) and CYP2C19 ((+)N-3-benzylnirvanol) inhibited formation of metabolites by <10%, suggesting that CYP3A4 plays the predominant role in metabolism of tofacitinib in humans.

In vitro studies using human recombinant CYP450 isoforms indicated that tofacitinib is primarily metabolized by CYP3A4 and CYP2C19 with minimal metabolism by CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2D6, CYP2E1, and CYP3A5. Human DDI studies have further confirmed the role of CYP3A4 in the clearance of CP-690,550 (see section on interactions).

A composite mass balance model was derived from human and *in vitro* data to aid in the understanding of tofacitinib ADME properties as shown in Figure 6 below.

Figure 6 - Mass Balance Model for CP-690,550 Following Oral Administration



The composite mass balance consolidates information from a number of different studies. The model, derived from *in vitro* data and studies in healthy volunteers, attributes approximately 30% of drug clearance to the renal elimination route and the remainder to hepatic elimination (70% of drug clearance).

Interconversion

At the conclusion of the re-examination, there was an outstanding concern in relation to whether tofacitinib may undergo stereoconversion *in vivo* that might in turn lead to off-target effects.

Tofacitinib is synthesised as the 3R,4R enantiomer with less than 0.2% of alternative stereoisomeric forms in the API. Only the 3R,4R enantiomer has pharmacological activity at JAK kinases. In response to concerns raised during the last procedure, the applicant has now developed bioanalytical methods, suitable for analysis of clinical PK samples, that are specific to the three alternative stereoisomeric forms (3R,4S; 3S,4R; and 3S,4S) to exclude the possibility of in vivo stereoconversion.

Representative steady state clinical samples from 14 RA subjects dosed with tofacitinib 5 mg b.i.d. were subjected to stereoisomer-specific assay. The 3R,4S; 3S,4R;and 3S,4S were all reported to be undetectable, the limit of the assay being capable of detecting 1% of the alternative stereoisomers relative to parent tofacitinib (the 3R,4R enantiomer). It can be concluded that, in line with the predictions from *in vitro* data, relevant in vivo stereoconversion does not occur.

Possible consequences of genetic polymorphism

In order to understand the relative contribution of CYP2C19 to the clearance of tofacitinib, genotyping was done in Study A3921028 which compared poor, extensive and ultra-extensive CYP2C19 metabolisers. Results indicated that CYP2C19 plays a relatively minor role in tofacitinib clearance and there is no need to adjust dose on the basis of CYP2C19 genotype.

Dose proportionality and time dependencies

Overall, tofacitinib PK is characterized by rapid absorption (Tmax of approximately 0.5-1 hours) and rapid elimination (t1/2 of approximately 3 hours) with no evidence of dose dependency.

Dose proportionality up to 10 times 5 mg is observed with no evidence of time dependent accumulation on initiation of twice daily dosing.

Special populations

Impaired renal function

No dedicated PK studies were conducted in RA patients with renal impairment. Non-RA subjects with all grades of renal impairment were studied, including those with end stage renal disease. Population PK data from RA subjects with mild and moderate renal impairment were compared with data from non-RA subjects in the dedicated renal impairment studies. RA patients with severe renal impairment were excluded from all clinical trials. Dose recommendations in this subgroup are informed by extrapolation from dedicated studies in non-RA subjects with severe renal impairment.

RA patients with mild and moderate renal impairment appear to exhibit a relatively modest increase in tofacitinib AUC of 8% (90% CI 4%,15%) and 29% (90%CI 15%,61%) respectively.

Tofacitinib dose is recommended to be reduced to 5 mg once daily in patients with severe renal impairment (<30 mL/min) given that there is an approximate two fold increase in tofacitinib AUC in this patient population and that patients should remain on a reduced dose even after haemodialysis.

Impaired hepatic function

RA patients with hepatic impairment were excluded from all clinical studies. Non-RA subjects with mild and moderate hepatic impairment were investigated in a dedicated PK study. No subjects with severe hepatic impairment were studied.

In subjects with mild hepatic impairment (Child Pugh A) tofacitinib mean AUC and Cmax ratios were within 3% of those in subjects with normal hepatic function. In contrast, in subjects with moderate hepatic impairment (Child Pugh B) there was a 65% increase in tofacitinib AUC∞ (90% CI 24.95%, 116.75%) and a 49% increase in Cmax (90% CI 12.26%, 97.11%). Tofacitinib was not evaluated in subjects with severe hepatic impairment as this was not considered a viable therapeutic option in RA patients due to the known importance of hepatic metabolism to the clearance of tofacitinib and the increased risk of serious consequences from immunosuppression in such patients.

No dose adjustment is recommended in RA patients with mild hepatic impairment but the dose is recommended to be reduced to 5 mg q.d. in patients with moderate hepatic impairment.

Gender

No dose adjustment on the basis of gender is required.

Race

The updated population PK analysis generally supports the lack of need for dose adjustment in different races. There is an ongoing study to detect potential differences in the PK/PD profile of Japanese patients leading to an altered safety profile.

Although there appears to be a reduction in exposure in African American patients (~20% reduction in AUC), efficacy analyses using continuous variables rather than binary variables indicate that a dose of 5 mg b.i.d. is effective in African American patients.

Body weight

Consistent with the single compartment model, low body weight (40kg) is associated with high Cmax and conversely, high body weight (140 kg) with low Cmax. The Applicant justifies the importance of Cave to

efficacy, and although body weight-dependent differences in Cmax might influence the toxicity profile, evidence from the lowest quartile of body weight indicates that any effect of body eight is modest.

Elderly

Population PK analysis evaluated the effect of age on the PK of tofacitinib. The analysis included 165 elderly (≥65 years) and 905 non-elderly (<65 years) subjects. Visual predictive checks (VPCs) demonstrated that the model adequately described the data by age (PMAR-00297). The full model indicated that an elderly subject 80 years of age had a 2% lower CL/F relative to a typical 55 year old subject, with 90% CI excluding a ≥10% decrease. In terms of V/F, a typical elderly subject 80 years of age showed an 11% lower typical V/F compared to a 55 year old subject. When analysed as two groups (elderly vs. non-elderly), geometric mean Cmax (121 vs.116 ng/mL) and Cav (45.2 vs. 42.2ng/mL) were approximately 4% and 7% greater, respectively, in elderly subjects. Similar results were observed with the inclusion of additional PK data from the ongoing LTE study (PMAR-00297).

Paediatrics

A PIP has been embarked on and all obligations, in scope, have been met to date as demonstrated by 2 successful partial PIP compliance checks completed in August 2011 and August 2015 and the relevant documentation has been supplied. A further partial PIP compliance check for tofacitinib was submitted on 04 January 2016. This partial PIP compliance check relates to Clinical Measure 5 (Study A3921103); a multiple dose pharmacokinetic (PK) study in children from 2 to less than 18 years of age with Juvenile Idiopathic Arthritis. A positive outcome was communicated by the PDCO on 26th February 2016 and the relevant documentation has been supplied.

Intra- and inter-individual variability

Estimates indicate that both intra-subject (%CV of approximately 5-7% for AUC(0-inf) and 12-25% for Cmax) and inter-subject variability (19-26% for AUC(0-∞) and 11-28% for Cmax) are modest.

Pharmacokinetics in target population

An updated population PK analysis was requested during the last procedure to further evaluate the role of intrinsic and extrinsic factors on tofacitinib PK.

The objectives of the updated analysis were to:

- Provide updated fixed and random effects parameter estimates given the additional study data
- Refine estimates of covariate effects given the additional patients
- Elucidate any time-dependent changes in tofacitinib CL/F and
- Investigate the effects of changes in hepatic function (using ALT as a surrogate) and renal function (using CLcr, calculated by Cockcroft-Gault equation)

Analysis of change in tofacitinib oral CL/F over time demonstrated an increase from 19 L/h at treatment initiation to a plateau of 20.9 L/h after 6 months of treatment.

Furthermore, a change in baseline ALT >x2 or a decrease in CLcr > 30% from baseline did not significantly affect tofacitinib CL/F.

The population PK of tofacitinib was described by a one-compartment model with zero-order absorption.

Justification for extension of the conclusions of the updated population PK analysis (which centred on a tofacitinib dose of 10 mg b.i.d.) to a 5 mg b.i.d. dosing regimen has been provided. In the original analysis,

inferences were made based on a population pharmacokinetic (PK) analysis covering a 30-fold dose range (1 to 30 mg twice daily [BID]), showing tofacitinib PK to be dose proportional. In the updated analysis, PK data from patients receiving either 5 (n=295) or 10 mg (n=745) BID in the ongoing long-term extension (LTE) study) were appended to the original dataset, with the primary purpose of evaluating whether tofacitinib oral clearance (CL/F) showed time dependency during long-term dosing. Thus both the original and updated analyses included patients taking 5 mg BID. The results indicated that the change in tofacitinib CL/F over time in the overall population demonstrated a small (~10%) increase to a plateau after 6 months of tofacitinib treatment. The assessment was performed under the assumption that any time dependency in CL/F would be dose-independent. However, a similar degree of enzyme recovery over time may lead to a proportionally greater increase in clearance. The Applicant has evaluated the potential for dose dependency within the assessment of time-dependency in tofacitinib CL/F. Consistent with the original and updated analyses, the new analysis has also shown no meaningful changes in tofacitinib CL/F upon chronic dosing for the 5 mg BID dose.

One apparent difference between the original model and the time dependent clearance model was in the African American population in which there was an approximate 25% increase (effect estimate of 1.24 (90% CI 1.07, 1.38) in CL/F when compared to Caucasians with a corresponding ~20% reduction in AUC. Further efficacy analyses (using continuous rather than binary variables) across racial subgroups have been provided which indicates that tofactinib at 5 mg b.i.d. is effective in African American population patients.

Although the single compartment model gives rise, to opposing effects on V/F and Cmax in relation to body weight, Cmin compensates for this so Cav values are unaffected. There is a large increase in apparent volume of distribution in patients with body weight ~ 140 kg, in contrast to oral clearance CL/F and Cav which are unaffected. The Applicant justifies the use of Cav to enable extrapolation of efficacy between subpopulations.

Consistent with the single compartment model, low body weight (40kg) is associated with high Cmax and conversely, high body weight (140 kg) with low Cmax which could influence the toxicity profile. Adverse events by quartiles of body weight have been analysed and although there are some increases in the lowest weight quartile, the increases are modest and not sufficient to warrant dose adjustment.

In the updated analysis, change in CL/F over time in the overall population demonstrated a small (~10%) increase to a plateau after 6 months of tofacitinib treatment. Suppression of the inflammatory state may lead to recovery in drug CYP450 metabolising enzyme activity and therefore, potentially increased drug clearance over time. Whilst there was a small increase in clearance, CYP450 enzyme activity presumptively does not recover in line with improvement in inflammatory state.

As requested in the previous procedure, the updated population PK analysis also includes data on potential effect on tofacitinib CL/F with changes in renal and hepatic function over time. The potential influence of changes in ALT and CLcr (from baseline) was examined in population subgroups where subjects were dichotomised into those with ≤ 30% or >30% decrease in CLcr from baseline, and those with values ≤ 2 or >2 times the baseline in ALT. Even a change in baseline ALT >x2 or a decrease in CLcr > 30% from baseline did not significantly affect tofacitinib CL/F.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials*	242/1710**	21/1710	0/1710

*Represents RA patients with PK data from Phase 2 and LTE studies (PMAR-00297);
**1710 is total number of patients with PK data; highest age in population PK analysis: 83 years

Pharmacokinetic interaction studies

In vitro

Potential for CP-690,550 to inhibit human drug metabolising enzymes in human liver microsomes

Incubations were conducted in the presence of probe substrates for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. At a concentration corresponding to steady state Cmax for a dose of 5 mg b.i.d. in RA patients, the Cmax/IC50 ratios were <0.005, suggesting a low potential for tofacitinib to increase plasma concentrations of co-administered drugs that are metabolised by CYP450 enzymes.

Potential for CP-690,550 to induce CYP3A4 and CYP1A2 in human hepatocytes

Treatment of primary human hepatocytes with tofacitinib resulted in modest induction (1.2-2.5-fold) of CYP3A4 mRNA but no induction of testosterone 6βhydroxylase activity (as a measure of catalytic activity of CYP3A4).

Evaluation of CP-690,550 as a substrate and modulator of the efflux transporters P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2)

Tofacitinib is not a substrate for BCRP.

Tofacitinib is a substrate of P-gp. However, the high oral bioavailability of tofacitinib (74%) indicates that its high P-gp-mediated efflux potential is largely overridden by its intrinsic good absorption properties. Clinically relevant interactions with efflux transporters are considered unlikely.

Evaluation of CP-690,550 as a substrate and inhibitor of renal and hepatic uptake and efflux transporters

On the basis of the data provided, there is an outstanding concern in relation to whether tofacitinib may act as an inhibitor of OAT1, OAT3 and MRP2 transporters. The Applicant has committed to provide an *in vitro* evaluation of the potential for Xeljanz to act as an inhibitor of OAT1, OAT3 and MRP2 as a post-authorization study.

Evaluation of CP-690,550 as an inhibitor of uridine diphosphate-glucuronosyltransferase (UGT) enzyme activity in human liver microsomes

The potential for tofacitinib to inhibit UGT (1A1, 1A4, 1A6, 1A9, and 2B7) enzyme activities in hepatic microsomes at tofacitinib concentrations was evaluated up to 100 µM. Given a steady-state unbound Cmax of ~112 nM for a dose of 5 mg b.i.d. in RA subjects, the [I]/IC50 ratios are ~0.001.

In vivo

Eight clinical studies evaluated drug-drug interactions with CP-690,550.

- The effect of other drugs on the PK of CP-690,550 was evaluated in the following studies: methotrexate (MTX) (A3921013), fluconazole (A3921014), tacrolimus (Tac) and ciclosporin (CsA) (A3921020), ketoconazole (A3921054) and rifampin (A3921056).
- The effect of CP-690,550 on the PK of other drugs was evaluated in the following studies: methotrexate (MTX) (A3921013), midazolam (A3921059), oral contraceptives (A3921071), and metformin (A3921143).

Overall, the findings confirm the importance of CYP3A4 and CYP219 in the metabolism of tofacitinib. The following changes were identified: Increases in AUC0-∞ with concomitant administration of fluconazole, tacrolimus (slight increase), ciclosporin and ketoconazole; increases in Cmax following administration of fluconazole and ketoconazole; decreases in Cmax and AUC following administration of rifampicin.

2.4.3. Pharmacodynamics

Mechanism of action

Tofacitinib binds deep within the ATP binding cleft of the JAK protein tyrosine kinase domain.

Tofacitinib exhibits the highest affinity for the JAK3 kinase (Kd 0.7nM) followed by JAK2 (Kd 2nM), JAK1 (3nM) and Tyk2 (250 nM). Tofacitinib has 2 chiral centres but only the 3R,4R enantiomer has pharmacological activity. In vivo stereoconversion has been excluded by stereoisomer-specific assays.

JAK3 is preferentially expressed in lymphocytes and mast cells and pairs with JAK1 to mediate the common γ chain cytokines, including interleukin (IL) 2, IL 4, IL 7, IL 9, IL 15, and IL 21, which are integral to lymphocyte activation, proliferation and function. Although JAK3 only pairs with JAK1 to mediate common γ chain cytokine signalling, JAK1 also pairs with JAK2 and TyK2 to transmit the signals of additional cytokines important in inflammation and immune responses including IL–6, IFNα and IFNγ. JAK can be considered to sit at a nodal point in the complex network of cytokine signalling, with far-reaching effects expected when JAK is inhibited.

Primary and Secondary pharmacology

Pharmacodynamic readouts of JAK inhibition demonstrate a hierachy of inhibitory responses in vivo over a time course consistent with STAT as an immediate downstream target and IP-10 and CRP as later steps in the pathway. Initial induction of PD effects are consistent with the PK but are more durable, supporting the twice daily administration of tofacitinib despite a short half-life of 3 hours.

Clinical studies support the durability of PD effects. The plasma concentration-time profiles over the range of tofacitinib doses in clinical studies where efficacy is demonstrated in rheumatoid arthritis reveal that IC50 values for JAK1/2/3 are attained in plasma for only part of a 24 hour period with a twice daily administration regimen. Nonetheless, this translates into a durable pharmacodynamic effect on acute phase reactants and the composite efficacy endpoint DAS28-3(CRP) that lasts for at least 2 weeks after cessation of treatment. This suggests that sub-maximal, non-continuous inhibition of JAK-STAT is sufficient to interrupt a key effector pathway in the inflammatory response in rheumatoid arthritis.

In the rodent collagen induced arthritis model the estimated Cavg value producing 50% of maximum effect was 28 ng/ml (95% CI 5.9-50), which is comparable to the mean Cavg for 5 mg b.i.d. dose (21 ng/ml) in RA patients.

Exposure relevant for safety

Human exposures used in calculating safety multiples were based on the results from the population pharmacokinetic modelling of tofacitinib in rheumatoid arthritis patients. The Applicant has made appropriate safety margin clarifications in Sections 4.5 and 5.3 of the SmPC.

There is an inverted U relationship between tofacitinib dose and haemoglobin postulated to be due to improvement in anaemia due to general improvement in the patient's condition with an opposing suppression of haemoglobin possibly due to JAK2-mediated inhibition of erythropoiesis. There doesn't appear to be a clear exposure-response relationship but overall safety data do not indicate anaemia to be a safety concern of note.

Tofacitinib treatment is associated with rapid and reversible decreases in absolute neutrophil count (ANC) in RA subjects, which stabilise by 3 months. Decreases are also seen with adalimumab and methotrexate (MTX). No subject developed a confirmed ANC of <500 cells/mm3 and there was no evidence of an association between low ANC and infection. In view of the theoretical induction of harmful neutropenia, initiation of tofacitinib is not recommended in subjects with ANC <1000 cells/ mm3. In addition, during treatment, confirmed subjects with ANC 500 - <1000 cells/mm3 should be temporarily taken off treatment until ANC rises to above 1000 cells/mm3. Subjects with a confirmed ANC of <500 cells/mm3 should be discontinued from tofacitinib therapy.

A similar approach to reductions in absolute lymphocyte count (ALC) is taken, with the exception that temporary interruption of treatment where ALC is 500 - <750 cells/mm3 is recommended and discontinuation if ALC is confirmed to be below 500 cells/mm3. Treatment should not be initiated where ALC is less than 750 cells/mm3.

LDL-c levels increased during tofacitinib treatment in the Phase III studies by a mean of 13.4% increase from baseline for the 5 mg b.i.d. dose. There is no evidence of a progressive increase in LDL-c in LTE studies. Investigation of covariates indicated that subjects with hyperlipidaemia at baseline showed smaller maximal increase.

A Cholesterol and Lipoprotein Kinetics Study A3921130 has been submitted with this application (see secondary pharmacology). The study was conducted in healthy volunteers and RA patients. This was a Phase 1 open-label mechanism-of-action study. Cholesterol and lipoprotein kinetics were assessed with 13C-cholesterol and 13C-leucine infusions. RA subjects were re-evaluated after receiving oral tofacitinib 10 mg twice daily for 6 weeks. The conclusion from this was that HDL cholesterol levels, which are depressed in RA patients, become normalised towards those in the healthy volunteer group on tofacitinib treatment. The rise in HDL cholesterol (an anti-atherogenic response) will tend to offset the risk of any potential rise in LDL-c.

Serum creatinine increases by 8.2 – 9.6% above baseline at tofacitinib 5 mg b.i.d. to reach steady state levels in ~6 weeks. The increases are reversible

Across the Phase II dose response studies, there was an incidence of <1% of ALT elevations >3 times the ULN. Across the Phase II/III studies combination of tofacitinib with MTX increased the risk of ALT elevation compared with tofacitinib as monotherapy. There was also a higher incidence of ALT elevation in MTX compared with tofacitinib treated patients. Routine liver function test monitoring is recommended along with routine haematology (SmPC section 4.4).

The results of Phase III studies are consistent with the model-predictions in that there was no relationship between tofacitinib therapy and clinically meaningful increases in blood pressure.

Exposure-response analysis indicated that the risk of serious infection increased with increasing exposure. Application of linear logistic models indicated that the 10 mg b.i.d. dose was estimated to have 1.3-1.9 times higher risk of serious infections compared to 5 mg b.i.d.

No clear association between tofacitinib exposure and risk of malignancy has been identified, although periodic skin examinations are recommended for patients at increased risk of skin cancer (SmPC section 4.4).

2.4.4. Discussion on clinical pharmacology

ADME

Oral absorption of tofacitinib, whether administered as single or multiple doses, is rapid and independent of dose. The mean plasma elimination half-life of tofacitinib is approximately 3.2 hours. Absolute bioavailability is 74%. This is consistent with the ADME study (A3921010) showing that tofacitinib absorption extent is likely not greater than 85% supporting the claimed of class III BCS.

All oral formulations used in the clinical development programme can be considered to be bioequivalent.

Tofacitinib is recommended to be given with and without food.

Low to moderate protein binding suggests low potential for drug interactions due to drug displacement.

In vitro and in vivo studies indicate that tofacitinib is extensively metabolized. All human circulating and excreted metabolites are present in animal species. The unresolved metabolites in plasma were not considered to be of concern. It would be expected that the metabolites present in urine would constitute a larger percentage. However, this of no concern since the elimination routes have been well characterised in in vitro studies and major CYPS responsible for tofacitinib metabolism have been identified.

Dose proportionality up to 10 times 5 mg is observed with no evidence of time dependent accumulation on initiation of twice daily dosing.

Overall, the DDI findings confirm the importance of CYP3A4 and CYP219 in the metabolism of tofacitinib. The SmPC appropriately describes the risk of increased exposure with co-administered strong CYP 3A4 inhibitors and dual CYP3A4/ CYP2C19 inhibitor drugs (see SmPC section 4.5).

Tofacitinib is a pharmacologically and clinically relevant substrate of the gastrointestinal efflux transporter P-gp, which will normally tend to reduced absorption. However, given the high oral bioavailability, dose linearity and lack of active secretion, Pgp does not appear to impact absorption. In summary, the data submitted indicates that P-glycoprotein inhibitors are unlikely to significantly affect the PK of tofacitinib.

There is a low likelihood that tofacitinib will influence the metabolism of co-administered drugs that are metabolised by UGT enzymes.

A composite mass balance model was submitted which helped in consolidating information from a number of different studies, showing that approximately 30% of drug clearance is due to the renal elimination route and the remainder to hepatic elimination (70% of drug clearance).

An updated population PK analysis was requested during the last procedure to further evaluate the role of intrinsic and extrinsic factors on tofacitinib PK.

Overall, the results are similar to those obtained from the original analysis. There are no meaningful changes in systemic exposure that warrant dosage adjustment for demographic factors.

The African American population demonstrated lower AUC due to an approximate 25% increase in CL/F. However, further efficacy analyses were provided which indicates that tofacitinib 5mg bid is effective in this population.

The population PK modelling approach, including the updated population PK analysis, is endorsed.

Justification for extension of the conclusions of the updated population PK analysis (which centred on a tofacitinib dose of 10 mg b.i.d.) to a 5 mg b.i.d. dosing regimen has been be provided. In light of the separate analysis on the 5 mg BID data, the % of change in CL/F over time with the 5 mg BID seems smaller if compared to the 10% increase in CL/F estimated on the totality of data over time. The Applicant has provided simulations to show the expected time dependency for 5 mg compared to 10 mg. This shows that 5 mg would be expected to behave similarly to 10 mg

Although the single compartment model gives rise, as expected, to opposing effects on V/F and Cmax in relation to body weight, Cmin compensates for this so Cav values are unaffected. The applicant was requested to justify the importance of Cav to efficacy of tofacitinib for it to be accepted as a critical parameter in the population PK analysis. The applicant provided new analysis to support the use of Cave based on: 1, the dynamics of the clinical response and the delay of action, 2, the PK drivers of efficacy which shows AUC_{24} drives efficacy better than C_{min}, 3, exposure response modelling which further supports Cave and 4, non-clinical data. This new analysis was considered acceptable to justify the use of Cav to enable extrapolation of efficacy between subpopulations.

Modest changes in renal and hepatic function in response to tofacitinib, provided these stabilise and do not deteriorate further, do not require dose adjustment. In some patients however, more serious transaminase elevation and drug induced liver injury do occur and are currently listed as an Important Identified Risk in the summary of safety concerns in the RMP. Along with routine haematology monitoring every 3 months, routine liver function test monitoring is also recommended along with appropriate additional precautionary measures which are included in section 4.4 of the SmPC. The section in 4.2 on Special Populations, renal and hepatic impairment, discusses dose reduction to 5 mg once daily in patients with pre-existing severe renal or moderate hepatic impairment which would also apply if patients were to deteriorate to severe renal impairment or moderate hepatic impairment (Child Pugh B) whilst on treatment.

Renal impairment

The recommendation to reduce tofacitinib dose to 5 mg once daily in patients with severe renal impairment (<30 mL/min) is endorsed given that there is an approximate two fold increase in tofacitinib AUC in this patient population. A lack of dose adjustment in patients with mild and moderate renal impairment is agreed.

Hepatic impairment

RA patients with hepatic impairment were excluded from all clinical studies. Non-RA subjects with mild and moderate hepatic impairment were investigated in a dedicated PK study. No subjects with severe hepatic impairment were studied. The proposed lack of dose adjustment in RA patients with mild hepatic impairment is endorsed. Dose reduction to 5 mg once daily is recommended in moderate hepatic impairment. Although there is some doubt about sufficiency of exposure with a 5 mg once daily dose in those with Child Pugh B hepatic impairment, given that drug induced liver toxicity is a known risk of tofacitinib, a potential risk of causing further deterioration in liver function in those who are already impaired would tend to support dose

reduction to 5 mg once daily. Patients with severe hepatic impairment (Child Pugh C) are included as a contraindication in section 4.3 in the SmPC.

Race

No dose adjustment based on Race is needed.

Elderly

No dose adjustment is needed in the elderly. Data in the elderly population of 75 years and over are limited. This is reflected in section 4.2 of the SmPC.

Children

A PIP in relation to juvenile idiopathic arthritis has been embarked on and all obligations, in scope, have been met to date.

Pharmacodynamics and exposure-response

Tofacitinib binds deep within the ATP binding cleft of the JAK protein tyrosine kinase domain when the PTK domain is in an "active" configuration which is postulated to explain in part the potency of its inhibitory effect. Cells in which JAK exists in an active or superactive state would be expected to be the most primed to respond.

In the rodent collagen induced arthritis model the estimated Cavg value producing 50% of maximum effect was 28 ng/ml (95% CI 5.9-50), which is comparable to the mean Cavg for 5 mg b.i.d. dose (21 ng/ml) in RA patients. Given the durability of pharmacodynamic effects in the face of fluctuant plasma concentrations it seems reasonable to use Cav (Cavg) or AUC to make inferences about potential efficacy benefit.

The possibility of a negative pharmacodynamic interaction between tofacitinib and MTX was raised but a co-exposure study in cultured primary cells to investigate effects on cytokines does not suggest this. Furthermore, tofacitinib in combination with MTX appears as effective as tofacitinib as monotherapy across all efficacy outcomes including structural preservation and in all patient subsets. Therefore, while an improved efficacy benefit with the combination may have been anticipated from predictions of potential additive effects on cytokine inhibition, this does not appear to be the case but there is also no clear signal of negative clinical efficacy interaction.

2.4.5. Conclusions on clinical pharmacology

Tofacitinib demonstrates an overall favourable clinical pharmacology profile to support its use in the treatment of rheumatoid arthritis.

On the basis of the data provided, there is an outstanding concern in relation to whether tofacitinib may act as an inhibitor of OAT1, OAT3 and MRP2 transporters. The CHMP recommended that an *in vitro* evaluation of the potential for Xeljanz to act as an inhibitor of OAT1, OAT3 and MRP2 shall be performed as a post-authorization study.

2.5. Clinical efficacy

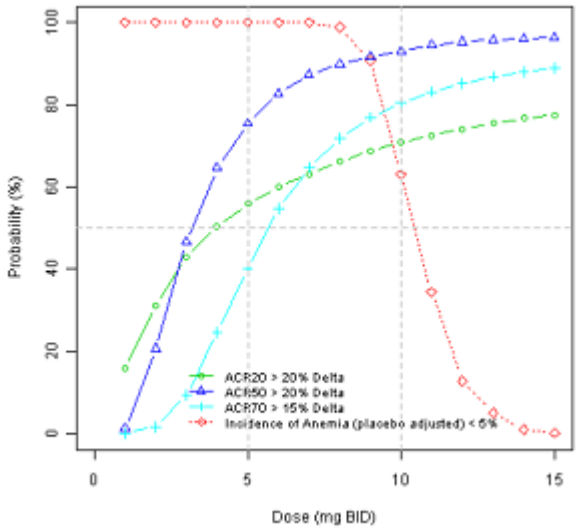
The application contains six Phase III studies, seven Phase II studies and 2 long-term extension (LTE) studies. All Phase II and Phase III studies were randomized, multi-centre, double-blind, parallel group studies; both extension studies were open label.

2.5.1. Dose response studies

Dose selection was primarily based on data from the Phase II study A3921025 because it was the most comprehensive in terms of dose range (1-15 mg b.i.d. doses) and duration (24 weeks) of treatment, and most representative of the planned Phase III programme. A review of several efficacy and safety outcomes from A3921025 was performed to identify key drivers for dose selection. For efficacy, the ACR endpoints were deemed to be the key measures of effects on signs and symptoms. A review of the safety data suggested dose responsiveness for haemoglobin levels (and associated anaemia incidence) and LDL-c. Dose selection would be primarily driven by ACR20, ACR50 and ACR70 response rates for efficacy and changes in haemoglobin (and associated incidence of anaemia) for safety. Dose selection was principally based on the probability of achieving a clinically meaningful target effect (PTE) for the selected safety and efficacy endpoints. This process took into account the clinical relevance of the magnitude of effect, the desired level of confidence in the target effect size, and the sampling variability in the dose-response profile. For each endpoint, the target effect was defined in terms of a placebo-adjusted response at, or through, a specific time point that was considered clinically meaningful. The target effect sizes for ACR20, ACR50 and ACR70 response rates were set at placebo-adjusted response rates of at least 20%, 20%, and 15%, respectively, at Week 12. Similarly, the acceptable threshold for >2 g/dL decrease from baseline or an absolute haemoglobin level of <8.0 g/dL was set at a placebo-adjusted incidence of no more than 5% through 24 weeks of exposure.

The PTE values for the three ACR endpoints and incidence of anaemia across doses of 1 to 15 mg b.i.d. are shown in Figure 7. Doses that were considered for Phase III were those that achieved a PTE of approximately 50% or higher on all four endpoints. The 5 and 10 mg b.i.d. doses met these criteria and were therefore selected for further evaluation in the Phase III programme. The inclusion of 10 mg b.i.d. in the Phase III programme reflected the possibility of increased benefit over the 5 mg b.i.d. dose on ACR70 (80% PTE for 10 mg b.i.d. vs 40% for 5 mg b.i.d.) while still maintaining >50% probability of having an acceptable incidence of anaemia.

Figure 7 – Probability of achieving target effects for efficacy (ACR20, ACR50 and ACR70 response rates) and safety (anemia) endpoints based on dose-response modelling of A3921025 data



Study A39210353 was another 24-week, Phase IIb study of tofacitinib administered as monotherapy after prior washout of all background DMARDs, which further supported the dose selection rationale. The study demonstrated dose response for ACR20, ACR50 and ACR70, with the lowest response rate (difference from placebo at Week 12) in the 1 mg b.i.d. group and the highest response rate in the 10 mg and 15 mg b.i.d. groups.

Exposure-efficacy response relationships in diverse RA patient populations:

A more comprehensive analysis of the efficacy and safety of tofacitinib across the Phase II programme was undertaken to inform an understanding of the exposure – efficacy response relationships in diverse RA patient populations.

Five (5) Phase II studies provided dose response information in populations of inadequate responders to disease modifying anti-rheumatic drugs (DMARDs), including 3 monotherapy studies (A3921019, A3921035 and A3921040) and 2 background MTX studies (A3921025 and A3921039). Studies A3921039 and A3921040 were performed in Japanese RA patients while the others were global and thus not restricted to any particular geographical region or ethnic group.

Dose-response profiles for proportions of ACR20, ACR50 and ACR70 responders and mean DAS28-3(CRP) were compared across studies at Week 12. In all 4 studies, there was clear evidence of dose response for each endpoint.

ACR assessments incorporate a series of measurements: the tender/painful joint count; the number of swollen joints; patient's assessment of pain (VAS); Patient's global assessment of arthritis; CRP or ESR (acute phase reactant); and the Health Assessment Questionnaire-Disability Index (HAQ DI) score.

ACR20, ACR 50 and ACR 70 responses reflect 20%, 50% and 70% improvements from baseline, respectively, in both swollen and tender joint count and in at least 3 of the 5 additional measures from the core ACR data set. The ACR scores therefore reflect relative and not absolute improvements. The respective ACR response

rates reflect percentage of patients who have reached or exceeded this threshold of response at a particular time point. ACR20 is recognised as a sensitive measure of improvement from baseline that will provide an early readout of non-response which is of value in placebo controlled trials of rheumatoid arthritis so that patients can be switched to active treatment. Across the Phase II and also the Phase III studies, patients in the placebo groups who did not meet the ACR20 threshold after 3 months were considered non-responders and were switched to active treatment (tofacitinib). This is in line with the most recent EULAR guidance (2013). Given that the primary analysis for the principal dose-response study A3921025 was conducted after 3 months, the analysis will not have been confounded by advancement to active treatment in the placebo group. Nonetheless, 3 months is a relatively early time point for evaluation of efficacy benefit.

ACR20 has the advantage that it may provide early detection of response before an agent has had time to exert a full therapeutic effect. Whereas ACR50 and ACR70 may have more ability to discriminate levels of therapeutic activity with efficacious doses.

In the principal dose-response study A3921025, DAS28-3(CRP) revealed a low threshold of response with even 1 mg b.i.d. demonstrating a separation from placebo at 12 weeks. This may reflect the relatively high contribution of C-reactive Protein (CRP) to the overall DAS score. Decline in CRP is an early response to many anti-inflammatory agents that inhibit cytokine signalling and may be particularly responsive to JAK-dependent IL signalling. As such, it is likely to be an early, sensitive indicator of successful inhibitory engagement of the JAK-STAT pathway but it may over-estimate the likelihood of an actual efficacy benefit.

Variability in efficacy response in the Phase II studies does not appear to be due to variability in exposure. The variability is likely to be contributed to by the relatively early time point (12 weeks) of the primary analysis in most of the Phase II studies, at which point the drug is likely to have sub-optimal therapeutic efficacy in many patients, particularly in the more stringent efficacy outcome measures, and especially in those more severely affected patients.

2.5.2. Main studies

Methods

Study Participants

The tofactinib in rheumatoid arthritis clinical study programme was designed prior to the updated 2010 ACR/EULAR criteria. Patients were therefore enrolled in the programme in accordance with the previous 1987 ACR classification criteria which were focused more on differentiation of rheumatoid arthritis from other types of inflammatory arthritis and as such, identified patients with established disease. Patients were required to have radiographic evidence of erosions typical of RA or of this was not available, positive serology (+RF and/or +anti-CCP). Patients in all studies, bar one, were required to have a minimum of 6 swollen joints and to have high levels of an acute phase reactant - either ESR > 28 mm/hr and/or C-reactive protein >7 mg/dL. Patients were also required to meet a minimum of Class III (ability to perform usual daily self-care) in the ACR 1991 revised criteria for global functional status in RA (Hochberg et al 1992 *Arthritis Rheum* 35:498-502).

The existence of characteristic erosions is prime facie evidence of RA. In the absence of radiographic evidence, patients were required to have positive serology (+RF and/or +anti-CCP). Patients would therefore clearly fall under a diagnosis of rheumatoid arthritis.

Patients were required to have no evidence of active, latent or inadequately treated TB infection: within 3 months of screening, a negative QuantiFERON-TB Gold In-Tube (QFT) test or, if unavailable, a Mantoux skin test, along with a chest radiograph showing no evidence of active TB, and no history of either untreated or inadequately treated latent or active TB infection. Patients were also required to have no history of recurrent or disseminated herpes zoster. Patients were not to receive any live vaccines within 6 weeks of commencement or discontinuation of study drug. Patients with any history of malignancy other than successfully treated non-melanoma skin carcinoma were excluded.

Treatments

Patients in studies that compared 5 mg b.i.d. with 10 mg b.i.d. received two tablets twice daily – made up of tofacitinib and a matched placebo tablet in the case of the 5 mg dosing arm. Although there is a reduction in Cmax in the presence of food, exposure is equivalent in the presence or absence of food.

In the adalimumab active comparator study adalimumab was given in accordance with the recommended EU posology (40 mg every other week i.e. QOW), in combination with background MTX, and is allowed to be self-administered by the patient if adequately trained.

In the MTX active comparator study (tofacitinib monotherapy) A3921069, MTX in the comparator arm was administered in combination with folic or folinic acid at up to 20 mg once a week, progressing from 10 mg and 15 mg after intervals of 4 weeks, if tolerated.

In 5 Phase III studies, subjects were randomized to treatment sequences as shown in Table 9. In each of these studies, a subject "advanced" from dosing Period 1 to Period 2. Advancement was mandatory at Month 3 for all subjects in 6-month Studies A3921032 and A3921045. In longer term Studies A3921044, A3921046 and A3921064, only nonresponders were advanced to Period 2 at Month 3, with the remaining subjects advancing at Month 6. This advancement scheme limited the time placebo-treated subjects were without active therapy. Only placebo-treated subjects actually changed study medication; subjects receiving tofacitinib blindly advanced to the same study treatment. Schematics for the treatment advancement are shown in Figure 8.

A "non-responder" subject was specifically defined as a subject who failed to improve at Month 3 by at least 20% from baseline in the number of swollen and tender/painful joints. Regardless of study and regardless of whether mandatory or not, advancement was always executed in a blinded fashion according to the sequence to which the subject was randomized at baseline.

Subjects in Study A3921069 were randomized to tofacitinib 5 mg b.i.d., tofacitinib 10 mg b.i.d., or MTX and remained on that treatment throughout their participation in the study.

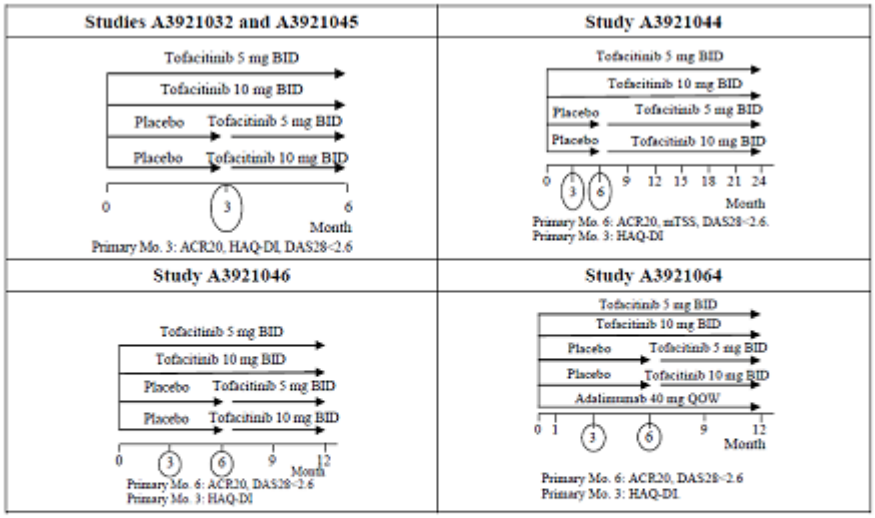
Table 9 - Randomization sequences in the phase 3 studies requiring treatment advancement

Treatment Sequence		Applicable Studies
Period 1	**Period 2**	
Tofacitinib 5 mg BID	Tofacitinib 5 mg BID	A3921032 A3921044 A3921045 A3921046 A3921064
Tofacitinib 10 mg BID	Tofacitinib 10 mg BID	
Placebo BID	Tofacitinib 5 mg BID	
Placebo BID	Tofacitinib 10 mg BID	
Adalimumab 40 mg, QOW SC injection	Adalimumab 40 mg, QOW SC injection	A3921064

Source: Protocols for Studies A3921032, A3921044 A3921045, A3921046, A3921064.
QOW=every other week, SC=subcutaneous, BID=twice daily, mg=milligram.

For reporting purposes, treatment groups reported as tofacitinib 5 mg or 10 mg bi.d. include subjects randomized to receive those study treatments. Unless indicated otherwise, the placebo treatment group includes subjects randomised to either of the 2 placebo treatment sequences (placebo advanced to tofacitinib 5 mg b.i.d and placebo advanced to tofacitinib 10 mg b.i.d) combined into a single placebo group.

Figure 8 – schematic for treatment sequences in phase 3 studies requiring treatment advancement



Source: Statistical Analysis Plan for Studies A3921032, Year 1 A3921044, A3921045, A3921046, A3921064.
Advancement time points are circled: Month 3 for all subjects in Studies A3921032 and A3921045; Month 3 for non-responders in Studies A3921044, A3921046 and A3921064 and all remaining subjects at Month 6.
The DAS28 variable is DAS28-4(ESR).
mTSS=modified total Sharp score, ACR20=American College of Rheumatology ≥20% improvement, DAS28=disease activity score 28 joints, HAQ-DI=health assessment questionnaire disability index, Mo=month, QOW=every other week, BID=twice daily, ESR=erythrocyte sedimentation rate, mg=milligram.

The use of ACR20 to define "non-responders" at month 3 was appropriate and adheres to ethical practice. This is a sensitive outcome measure which, if it is not met in an individual, can be used to determine a switch to active treatment.

In study A3921044, radiographic data from placebo subjects following advancement to active treatment were subjected to linear extrapolation from the point at which advancement occurred. This is a recognised way to handle missing radiographic progression scores in RA trials and does not appear to over-estimate overall radiographic progression (Markusse et al ACR abstract 2014). This is therefore viewed as a valid way to manage missing radiographic progression scores which is relevant to placebo controlled RA trials where for ethical reasons patients are treated with placebo for a short duration only. The alternative of using the last available placebo observation would risk under-estimating the treatment effect. Other outcome measures (e.g. HAQ-DI, not suitable for extrapolation upon advancement to placebo) were scored as missing data in those who required early advancement.

Background treatments

Ongoing ("background") DMARD therapy varied in the Phase III studies. For Studies A3921032, A3921044, and A3921064, the background DMARD was specified to be MTX, whereas for Study A3921046, csDMARDs that are not potent immunosuppressive agents were allowed, including MTX, leflunomide, sulfasalazine, gold salts, penicillamine, antimalarials and combinations thereof. For monotherapy Studies A3921045 and A3921069, only background antimalarials were allowed. Background DMARD therapy was to remain stable during the study.

In studies where background MTX is given the MTX doses were generally at least 15 mg/week and no greater than 25 mg/week. MTX doses <15 mg/week were permitted for documented toxicity from or intolerance to higher doses or where higher doses would violate the local MTX label.

In study A3921069 MTX is commenced at a dose of 10 mg once weekly and increased to 15 mg and thence 25 mg per week if tolerated. Although there is some variation between different EU member states in the maximum recommended dose of MTX for rheumatoid arthritis, in clinical practice up to 25 mg per week can be given if a high dose is considered to be necessary.

Objectives

The tofacitinib RA clinical development programme was designed to demonstrate efficacy in reducing signs and symptoms of RA, inhibiting the progression of structural damage, and improving physical function, fatigue, and health related quality of life. The efficacy of tofacitinib in rheumatoid arthritis was investigated in a variety of settings relevant to 2nd line (MTX/csDMARD inadequately responsive), 3rd line (biologic inadequately responsive) and also 1st line (MTX naïve) treatment. The primary focus of the Phase III programme which consisted of 6 pivotal clinical studies was to assess the efficacy and safety of tofacitinib as a second line treatment in patients who had responded inadequately to a csDMARD, mostly methotrexate (MTX). Two studies also addressed tofacitinib administered as monotherapy (one in the first line setting and one in 2nd line).

Efficacy of tofacitinib was also compared with established standard of care drugs in two studies:

1. A3921064: as a secondary objective, to evaluate non-inferiority compared to the biologic therapy adalimumab, in the second line setting, both given in combination with background MTX.
2. A3921069: as a primary objective, to evaluate superiority in MTX naïve patients of tofacitinib as monotherapy compared to methotrexate as monotherapy, in the slowing of structural progression. The updated dossier contains study data to 24 months.

The pivotal clinical development programme was designed to address the efficacy and safety of tofacitinib in rheumatoid arthritis at two doses – 5 mg b.i.d. and 10 mg b.i.d. In the updated dossier, 5 mg b.i.d. is proposed as the maximum recommended dose in any population.

Outcomes / endpoints

Table 10 provides a summary of all pre-specified and post-hoc efficacy measures, used in primary or secondary endpoints. The pre-specified primary efficacy endpoints (Table 10) were variously prioritised according to the primary objective of the study.

Table 10 – Summary of all efficacy measures

Assessment	Endpoint
Signs and symptoms	ACR20, ACR50, ACR70, and individual components (SJC, TJC, PtAP, PtGA, PhGA, CRP, HAQ-DI)
Physical function	HAQ-DI
Composite disease activity measures	DAS28-4(ESR), DAS28-4(CRP), DAS28-3(ESR), DAS28-3(CRP), CDAI, SDAI
Boolean-based disease activity	Boolean 3, Boolean 4
Acute phase reactants	CRP, ESR
Joint damage progression: X-ray	mTSS, erosion component, JSN component, mTSS ≤ 0.5 unit change, erosion score ≤ 0.5 unit change
Patient Reported Outcomes	SF-36, WLQ, EuroQoL EQ-5D, MOS sleep scale, FACIT-fatigue scale

ACR20(50,70)=American College of Rheumatology ≥20% (≥50%, ≥70%) improvement, CRP=C-reactive protein, HAQ-DI=health assessment questionnaire disability index, DAS28=disease activity score 28 joints, ESR=erythrocyte sedimentation rate, MOS=medical outcomes study, CDAI=clinical disease activity index, SDAI=simple disease activity index, SJC=swollen joint count, TJC=total joint count, PtGA=patient global assessment, PhGA=physician global assessment, PtAP= patient assessment of arthritis pain, mTSS=modified total Sharp score, JSN=joint space narrowing, SF-36=short form 36 health survey, FACIT=functional assessment of chronic illness therapy, EuroQol EQ-5D=European Quality of Life 5-dimension scale, WLQ=work limitations questionnaire.

Table 11 provides established definitions of minimum clinically important difference and cut points for continuous composite measures of disease activity states:

Table 11 – minimal clinically important differences and categorical cut points for continuous measures of composite disease activity states or physical function

Disease Severity	Variable	Scores
Improvement	HAQ-DI	≥ 0.22
	DAS28-3(CRP)	≥ 1.2
	DAS28-4(ESR)	≥ 1.2
Low disease activity	DAS28-4(ESR)	≤ 3.2
	DAS28-3(CRP)	≤ 3.2
	DAS28-4(CRP)	≤ 3.2
	CDAI	≤ 10
	SDAI	≤ 11
Remission	DAS28-4(ESR)	< 2.6
	DAS28-3(CRP)	< 2.6
	DAS28-4(CRP)	< 2.6
	CDAI	≤ 2.8
	SDAI	≤ 3.3
	Boolean 3	Boolean-based remission requires scores ≤1 on all of these measures: TJC28 ≤1, SJC28 ≤1, CRP ≤1 mg/dL, PtGA ≤1 (0–10 scale; for Boolean 4)
	Boolean 4	

CRP=C-reactive protein, HAQ-DI=health assessment questionnaire disability index, DAS28=disease activity score 28 joints, ESR=erythrocyte sedimentation rate, CDAI=clinical disease activity index, SDAI=simple disease activity index, TJC28=tender joint count 28 joints, SJC28=swollen joint count 28 joints, PtGA=patient global assessment, mg=milligram, dL=decilitre.

Table 12 - Pre-specified primary efficacy endpoints in Phase III studies

	A3921032 3 line	**A3921044** 2 line	**A3921045** 2 line Monotherapy	**A3921046** 2 line	**A3921064** 2 line	**A3921069** 1 line Monotherapy
ACR20 Response Rate	Month 3	Month 6	Month 3	Month 6	Month 6	NA
ACR70 Response Rate	NA	NA	NA	NA	NA	Month 6
Change from Baseline in mTSS	NA	Month 6	NA	NA	NA	Month 6
Change from Baseline in HAQ-DI	Month 3	Month 3	Month 3	Month 3	Month 3	NA
Rate of DAS28-4(ESR) <2.6	Month 3	Month 6	Month 3	Month 6	Month 6	NA

NA=not applicable, ACR20(70)=American College of Rheumatology ≥20% (≥70%) improvement, HAQ-DI= health assessment questionnaire disability index, DAS28=disease activity score 28 joints, ESR=erythrocyte sedimentation rate, mTSS=modified total Sharp score.

Pre-specified secondary efficacy endpoints in the Phase III studies are summarised in the table below:

Table 13 - Pre-specified secondary efficacy endpoints in the Phase III studies

Endpoints	**Secondary Time Point[b]**	**Applicable Studies**
Signs and symptoms and physical function		
ACR20, ACR50, ACR70 responder rate	For ACR20, all except the primary ACR20 time point; for ACR50, all time points; for ACR70, all except Month 6 (primary) in Study A3921069.	All studies
Actual and change from baseline of the 7 separate ACR response components[a]	All time points	All studies
Durability of ACR20, ACR50, ACR70 response rates	All time points	A3921044, A3921046, A3921064, A3921069
ACR70 response for at least 6 Months	> 6 months	A3921044, A3921046, A3921064, A3921069
Rates of HAQ-DI change ≥0.22	All time points	All studies
Actual and change from baseline in DAS28-3(CRP) and DAS28-4(ESR)	All time points	All studies
Incidence of DAS28-4(ESR) <2.6	All except the primary time point	All except A3921069 where all time points were secondary
Incidence of DAS28-3(CRP) ≤3.2, DAS28-4(ESR) ≤3.2, DAS28-3(CRP) <2.6	All time points	All studies
Durability of DAS28 response rates	All time points	A3921044, A3921046, A3921064, A3921069
Joint structure		
Actual and change from baseline of erosion and JSN components of mTSS	Months 6, 12, 24	A3921044, A3921069
Proportion of non-progression in mTSS and erosion score (≤ 0.5 unit change)	Months 6, 12, 24	A3921044, A3921069
Change from baseline in mean mTSS	Months 12, 24	A3921044, A3921069
Patient reported outcomes		
Actual and change from baseline in the 1) SF-36 8 general health domain scores and 2 component scores, 2) WLQ 4 domain scores and the work loss index, 3) EuroQol EQ-5D, 4)MOS sleep scale, and 5) FACIT-fatigue scale.	All time points	All studies

Endpoints	Secondary Time Point[b]	Applicable Studies

ACR20(50, 70)=American College of Rheumatology ≥20% (≥50%, ≥70%) response, HAQ-DI=health assessment questionnaire disability index, mTSS=modified total Sharp score, JSN=joint space narrowing, CRP=C-reactive protein, DAS28=disease activity score 28 joints, ESR=erythrocyte sedimentation rate, MOS=medical outcomes study, FACIT= functional assessment of chronic illness therapy, SF-36=short form 36 health survey, EuroQol EQ-5D=European quality of life 5-dimension scale, WLQ=work limitations questionnaire, CSR=clinical study report.

a. 7 ACR response components are tender/painful joint count, swollen joint count, patient assessment of arthritis pain, physician global assessment of arthritis, patient global assessment of arthritis, CRP and HAQ-DI.

b. Based on all time points where data were collected as specified in each protocol.

Post-hoc efficacy analyses

A number of post hoc efficacy analyses were conducted to further understand and support the demonstration of the efficacy of tofacitinib in treating RA:

- Changes from baseline in the clinical disease activity index (CDAI) and the simple disease activity index (SDAI)
- Low disease activity (LDA) as defined by CDAI ≤10 and SDAI ≤11
- Remission as defined by CDAI ≤2.8, SDAI ≤3.3, Boolean 3 criteria, Boolean 4 criteria
- Improvement as defined by changes in DAS28-4(ESR) ≥1.2 and DAS28-3(CRP) ≥1.2
- Additional sensitivity analyses for structure for Study A3921044
- Assessment of efficacy in Study A3921044 based on prognostic risk factors and baseline CRP

Sample size

Study A3921044:

This study was powered at ~90% for all 4 endpoints in the step down hierarchy: ACR20 response rate, the preservation of joint structure as measured by mTSS, change in physical function by HAQ-DI and incidence of DAS28-4(ESR) <2.6 at 6 months. The sample size was determined on the basis of a simulation which accounted for the specific design of this study where placebo patients may have advanced at Month 3 or Month 6. Based on a simulation the design with 750 total patients randomized in a 4:4:1:1 ratio where the 2 placebo groups were combined (resulting in a 2:2:1 effective randomization) resulted in power of ~90% depending on different treatment effects and analysis methods.

A3921046

This study was powered at >90% for all three primary endpoints in the step-down hierarchy: ACR20, HAQ-DI and DAS28-4(ESR) <2.6

A3921064

This study was powered for all 3 endpoints in the step down hierarchy: ACR20 response rate at Month 6, physical function as measured by the HAQ-DI change from Baseline at Month 3, and incidence of DAS28-4(ESR) <2.6 at Month 6.

A3921045 (monotherapy, 2nd line)

This study was powered for all 3 endpoints in the step down hierarchy: ACR20 response rate, HAQ-DI and DAS28-4(ESR) <2.6.

A3921069 (monotherapy, 1st line)

The endpoint that determined the sample size for this study was the preservation of joint structure as measured by a modified Sharp score. The given sample size will provide 90% power, assuming a difference in mTSS of at least 0.9 unit (with a standard deviation [SD] of 2.8). For ACR70 analysis, the given sample size will yield over 90% power assuming a difference in response rates of at least 15% (with a MTX response of ~20%).

A3921032 (3rd line TNFi-IR)

Determination of sample size was driven by sample-size calculations made separately for each endpoint in the step-down hierarchy. The proposed sample size of 396 patients yielded:

- Over 90% power for the ACR20 analysis, the first endpoint in the step-down procedure, assuming a difference in response rates of at least 20% (with the placebo response at 30%) at Month 3;
- Over 90% power for the analysis of the HAQ-DI, the second endpoint in the step-down procedure, for differences of 0.3 or greater at Month 3, assuming a standard deviation of 0.75

Over 90% power for DAS28-4(ESR) <2.6, the third endpoint in the step-down procedure, assuming a difference in response rates of at least 15% (with the placebo response at 10%) at Month 3.

Randomisation

Table 14 - Summary of Randomization Scheme for Phase 3 Studies of Tofacitinib in Rheumatoid Arthritis

Protocol	Type of Randomization	Treatment Allocation	Block Size	Strata
A3921032	Double-blind, Central Randomization	Tofa 5 mg BID Tofa 10 mg BID Placebo → Tofa 5 mg BID Placebo → Tofa 10 mg BID (2:2:1:1)	6	South Korea, Rest of World
A3921044	Double-blind, Central Randomization	Tofa 5 mg BID Tofa 10 mg BID Placebo → Tofa 5 mg BID Placebo → Tofa 10 mg BID (4:4:1:1)	10	Japan, South Korea, Rest of World
A3921045	Double-blind, Central Randomization	Tofa 5 mg BID Tofa 10 mg BID Placebo → Tofa 5 mg BID Placebo → Tofa 10 mg BID (4:4:1:1)	10	None
A3921046	Double-blind, Central Randomization	Tofa 5 mg BID Tofa 10 mg BID Placebo → Tofa 5 mg BID Placebo → Tofa 10 mg BID (4:4:1:1)	10	China, Rest of World
A3921064	Double-blind, Central Randomization, Center-based	Tofa 5 mg BID Tofa 10 mg BID Placebo → Tofa 5 mg BID Placebo → Tofa 10 mg BID Adalimumab 40 mg q2w SC (4:4:1:1:4)	14	South Korea, Rest of World
Source: Randomization Schedule Request form and Impala Protocol Parameters Worksheet for each study, available on request; A3921032 CSR Section 6 and 9, A3921044 CSR Section 6 and 9 , A3921045 CSR Section 6 and 9, A3921046 CSR Section 6 and 9, A3921064 CSR Section 6 and 9 Abbreviations: Tofa=tofacitinib, BID=twice a day, mg=milligram, q2w=every 2 weeks, SC=sub-cutaneous				

Blinding (masking)

All 6 pivotal Phase III studies were double-blinded.

Statistical methods

The full analysis set included all patients who were randomised and received at least one dose of the randomised study drug. This was the primary analysis population. In addition for each endpoint the patient was required to have a baseline and at least one non-missing on-study assessment of that endpoint to be included in the analysis.

The safety analysis set was defined as those patients who were randomised to the study and received at least one dose of the study drug.

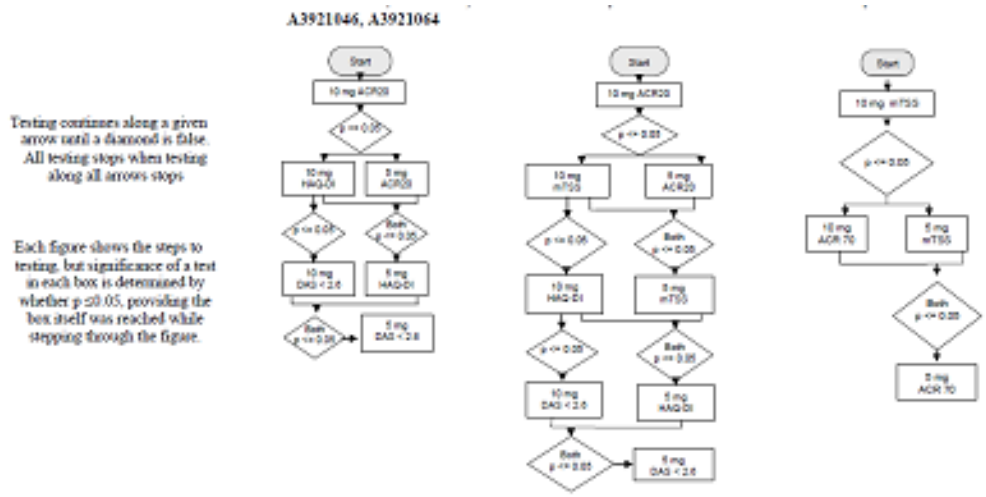
The definition of the full analysis set is acceptable for a double-blind trial.

Step-down hierarchy for primary endpoint evaluation:

In order to preserve Type I error in these studies with multiple primary endpoints, each objective was assessed sequentially using a step-down approach, where statistical significance was claimed for a given endpoint only if the prior endpoint in the sequence met the requirements for statistical significance.

Additionally, the step-down approach was applied for the 2 tofacitinib doses within each endpoint. At each endpoint, the tofacitinib 10 mg b.i.d. dose could only achieve statistical significance if the 10 mg b.i.d. dose at the prior endpoint was significant. The tofacitinib 5 mg b.i.d. dose could only achieve significance for each endpoint if both the 10 mg b.i.d. dose at the same endpoint and the 5 mg b.i.d. dose at the prior endpoint were significant.

Figure 9 – Primary analysis step-down procedure for Phase 3 studies



Source: Statistical analysis plans for Studies A3921032, Year 1 A3921046, A3921065, A3921046, A3921064, Year 1 A3921069.
All tofacitinib doses are twice daily.
ACR20(70)=American College of Rheumatology ≥20% (≥70%) improvement; HAQ-DI=health assessment questionnaire disability index; mTSS=modified total Sharp score; DAS=disease activity score 28 joints; mg=milligram.

The step down procedure is adequate to control the Type 1 error for the multiple primary endpoints and two drug doses. The ACR20 endpoint was analysed first in the hierarchy and therefore presumptively the endpoint considered of highest clinical relevance to the stated objectives of all the studies apart from A3921069. However, as discussed earlier, ACR20 is considered to lack stringency as a primary endpoint. Given that a marketing authorisation decision takes into account the overall benefit-risk profile of a product, a low stringency endpoint in a pivotal trial may not fully capture the efficacy benefit of a high performing product which has to be set against its risks. In order to assist the overall benefit-risk evaluation, statistical significance for ACR20 response rate would not be considered as sufficient on its own for the trial to be considered positive. Statistical significance will therefore be required for ACR20 and at least the next endpoint in the hierarchy, for the trial to be considered as having reached a positive outcome, depending on the objective of the study. In the context of the updated dossier, in which the maximum recommended dose is now 5 mg b.i.d. and not 10 mg b.i.d., statistical significance will need to be reached for the key primary endpoints at the 5 mg b.i.d. dose.

Results

Participant flow

Table 15 - Subject Disposition for Phase 3 Studies

	Number (%) of Subjects				
	Tofacitinib		Placebo → Tofacitinib		
	5 mg BID	10 mg BID	5 mg BID	10 mg BID	Active Comparator
Study A3921032					
Randomized	133	134	66	66	--
Treated	133	134	66	66	--
Completed	107 (80.5)	103 (76.9)	53 (80.3)	48 (72.7)	--
Died	0	0	0	1 (1.5)	--
Discontinuations related to study drug	10 (7.5)	12 (9.0)	6 (9.1)	8 (12.1)	--
Adverse event	8 (6.0)	7 (5.2)	3 (4.5)	0	--
Lack of efficacy	2 (1.5)	5 (3.7)	3 (4.5)	8 (12.1)	--
Study A3921044 Year 1					
Randomized	321	319	81	79	--
Treated	321	316	81	79	--
Completed	0	0	0	0	--
Ongoing at Year 1	250 (77.9)	265 (83.1)	64 (79.0)	64 (81.0)	--
Died	1 (0.3)	1 (0.3)	0	0	--
Discontinuations related to study drug	35 (10.9)	22 (7.0)	10 (12.3)	6 (7.6)	--
Adverse event	27 (8.4)	19 (6.0)	5 (6.2)	4 (5.1)	--
Lack of efficacy	7 (2.2)	3 (0.9)	3 (3.7)	1 (1.3)	--
Other	1 (0.3)	0	2 (2.5)	1 (1.3)	--
Study A3921044 Year 2					
Randomized	321	319	81	79	--
Treated	321	316	81	79	--
Completed	212 (66.0)	220 (69.0)	55 (67.9)	52 (65.8)	--
Died	4 (1.2)	1 (0.3)	1 (1.2)	0	--
Discontinuations related to study drug	47 (14.6)	44 (13.9)	13 (16.0)	12 (15.2)	--
Adverse event	36 (11.2)	37 (11.7)	8 (9.9)	10 (12.7)	--
Lack of efficacy	10 (3.1)	7 (2.2)	3 (3.7)	1 (1.3)	--
Other	1 (0.3)	0	2 (2.5)	1 (1.3)	--
Study A3921045					
Randomized	244	245	61	61	--
Treated	243	245	61	61	--
Completed	232 (95.1)	218 (89.0)	54 (88.5)	51 (83.6)	--
Died	0	1 (0.4)	0	0	--
Discontinuations related to study drug	4 (1.6)	7 (2.9)	5 (8.2)	5 (8.2)	--
Adverse event	3 (1.2)	6 (2.4)	2 (3.3)	1 (1.6)	--
Lack of efficacy	1 (0.4)	1 (0.4)	3 (4.9)	4 (6.6)	--

	Number (%) of Subjects				
	Tofacitinib		Placebo → Tofacitinib		
	5 mg BID	10 mg BID	5 mg BID	10 mg BID	Active Comparator
Study A3921046					
Randomized	318	318	79	80	--
Treated	315	318	79	80	--
Completed	261 (82.1)	252 (79.2)	71 (89.9)	67 (83.8)	--
Died	0	2 (0.6)	0	0	--
Discontinuations related to study drug	31 (9.8)	34 (10.7)	3 (3.8)	4 (5.0)	--
Adverse event	14 (4.4)	20 (6.3)	0	0	--
Lack of efficacy	16 (5.1)	12 (3.8)	3 (3.8)	3 (3.8)	--
Other	1 (0.3)	2 (0.6)	0	1 (1.3)	--
Study A3921064					
Randomized	204	201	56	52	204[a]
Treated	204	201	56	52	204[a]
Completed	150 (73.5)	158 (78.6)	47 (83.9)	39 (75.0)	162 (79.4)[a]
Died	0	0	0	0	1 (0.5)[a]
Discontinuations related to study drug	25 (12.3)	22 (10.9)	5 (8.9)	5 (9.6)	22 (10.8) [a]
Adverse event	19 (9.3)	15 (7.5)	2 (3.6)	2 (3.8)	16 (7.8)[a]
Lack of efficacy	6 (2.9)	7 (3.5)	3 (5.4)	3 (5.8)	6 (2.9)[a]
Study A3921069 Year 1					
Assigned to Study Treatment	374	398	--	--	186[b]
Treated	371	395	--	--	186[b]
Completed	0	0	--	--	0[b]
Ongoing at Year 1	307 (82.1)	328 (82.4)	--	--	134 (72.0)[b]
Died	0	0	--	--	0 [b]
Discontinuations related to study drug	28 (7.5)	24 (6.1)	--	--	29 (15.6)[b]
Adverse event	13 (3.5)	17 (4.3)	--	--	11 (5.9)[b]
Lack of efficacy	15 (4.0)	7 (1.8)	--	--	18 (9.7)[b]
Study A3921069 Year 2					
Assigned to Study Treatment	373	399	--	--	186[b]
Treated	373	397	--	--	186[b]
Completed	266 (71.3)	286 (71.7)	--	--	106 (57.0)[b]
Died	2 (0.5) +1	0 +1	--	--	0[b]
Discontinuations related to study drug	43 (11.5)	36 (9.1)	--	--	44 (23.7)[b]
Adverse event	23 (6.2)	25 (6.3)	--	--	18 (9.7)[b]
Lack of efficacy	20 (5.4)	11 (2.8)	--	--	26 (14.0)[b]

Subjects who died are not listed as discontinuations.
BID=twice daily, mg=milligrams, CSR=clinical study report.
a. Adalimumab 40 mg subcutaneously every other week.
b. Methotrexate.

Table 16 -Timing of Discontinuation in Phase 3 Studies

	Number of Subjects				
	Tofacitinib		Placebo → Tofacitinib		
	5 mg BID	10 mg BID	5 mg BID	10 mg BID	Comparator
Study A3921032 All placebo-treated subjects advanced to tofacitinib at Month 3.					
Randomized	133	134	66	66	--
Treated	133	134	66	66	--
Discontinued ≤ Month 3	15	12	7	13	--

	Number of Subjects				
	Tofacitinib		Placebo → Tofacitinib		
	5 mg BID	10 mg BID	5 mg BID	10 mg BID	Comparator
Discontinued > Month 3	11	19	6	5	--
Study A3921045 All placebo-treated subjects advanced to tofacitinib at Month 3.					
Randomized	244	245	61	61	--
Treated	243	245	61	61	--
Discontinued ≤ Month 3	4	13	5	9	--
Discontinued > Month 3	7	14	2	1	--
Study A3921044 Year 1Placebo-treated non-responders advanced to tofacitinib at Month 3; all remaining placebo-treated subjects advanced to tofacitinib at Month 6.					
Randomized	321	319	81	79	--
Treated	321	316	81	79	--
Advanced at Month 3	68	47	36	35	--
Discontinued ≤ Month 3	27	13	4	7	--
Discontinued Month 3-6	15	15	5	5	--
Discontinued > Month 6	29	23	8	3	--
Study A3921046 Placebo-treated non-responders advanced to tofacitinib at Month 3; all remaining placebo-treated subjects advanced to tofacitinib at Month 6.					
Randomized	318	318	79	80	--
Treated	315	318	79	80	--
Advanced at Month 3	67	40	37	35	--
Discontinued ≤ Month 3	19	20	3	5	--
Discontinued Month 3-6	21	27	4	4	--
Discontinued > Month 6	14	19	1	4	--
Study A3921064 Placebo-treated non-responders advanced to tofacitinib at Month 3; all remaining placebo-treated subjects advanced to tofacitinib at Month 6.					
Randomized	204	201	56	52	204[a]
Treated	204	201	56	52	204[a]
Advanced at Month 3	40	39	25	19	47[a]
Discontinued ≤ Month 3	15	15	4	9	12[a]
Discontinued Month 3-6	17	12	2	1	11[a]
Discontinued > Month 6	22	16	3	3	19[a]
Study A3921069 No treatment advancement					
Randomized	373	399	--	--	186[b]
Treated	373	397	--	--	186[b]
Discontinued ≤ Month 3	17	16	--	--	13
Discontinued Month 3-6	16	16	--	--	15
Discontinued > Month 6	76	86	--	--	52

BID=twice daily, mg=milligrams, CSR=clinical study report.
a. Adalimumab 40 mg subcutaneously every other week.
b. Methotrexate.

Baseline data

Demographic Characteristics

Table 17 - Baseline demographics for the Phase 3 studies

	A3921032	A3921044	A3921045	A3921046	A3921064	A3921069
Subjects treated	399	797	610	792	717	952
% Female	84.0	85.1	86.6	81.4	81.7	79.1
Mean (range) age in years	55.0 (20-84)	52.8 (18-82)	51.8 (21-81)	52.3 (18-86)	52.9 (18-83)	49.6 (18-83)
Race; White/Black/ Asian/Other; n	332/27/27/13	368/24/338/67	409/28/88/85	439/15/275/63	517/13/108/79	631/29/161/131
Mean (range) weight; kg	79.1 (43.0-188.0)	67.8 (36.2-159.2)	72.1 (30.5-157.0)	70.5 (34.7-186.9)	72.0 (34.5-162.0)	70.9 (31.4-183.2)

Includes all treatment groups in the studies.
n=number of subjects, kg=kilograms, CSR=clinical study report.

Baseline Disease Characteristics

Table 18 - Range of Mean Values Across Treatment Groups for Baseline Disease Characteristics in the Phase 3 Studies

	A3921032 N=399	A3921044 N=797	A3921045 N=610	A3921046 N=792	A3921064 N=717	A3921069 N=952
Mean disease duration (years)[a]	11.2-13.0	8.8-9.5	7.3-8.6	8.1-10.2	6.9-9.0	2.6-3.3
Rheumatoid factor antibody + (%)	60.6-70.8	75.2-79.7	47.5-71.3	72.2-73.9	60.8-71.4	81.5-84.4
Mean tender joint count	26.7-29.7	22.6-24.1	28.4-29.4	21.9-27.2	26.1-28.5	25.1-25.6
Mean swollen joint count	15.1-19.3	14.0-14.5	16.3-17.7	13.9-14.6	15.8-16.9	15.6-16.8
Mean HAQ-DI	1.50-1.66	1.23-1.41	1.48-1.58	1.24-1.45	1.36-1.53	1.50-1.54
Mean DAS28-4 (ESR)	6.29-6.59	6.25-6.34	6.61-6.71	6.14-6.44	6.33-6.56	6.54-6.61
Mean mTSS	NA	30.1-37.3	NA	NA	NA	16.5-20.3

N=number of subjects treated, NA=not applicable, HAQ-DI= health assessment questionnaire disability index, ESR=erythrocyte sedimentation rate, DAS28=disease activity score 28 joints, CSR=clinical study report, mTSS=modified total Sharp score.
a. Duration (years) from first diagnosis.

The mean patient age, 49-55 years old, reflected that of the target population.

Generally 60-80% of subjects were RF positive; a slight higher percentage was recorded in the A3921069 study due to inclusion criteria aimed to select subjects prone to develop bone damage.

Other baseline disease characteristics such as mean TJC, SJC, mean DAS-28-4(ESR) reflect the target population of active RA.

As expected, in studies with bone endpoints (A3921044 and A3921069) the mean mTSS at baseline was double in the MTX-IR study (30.1-37.3) than in the MTX-naïve (16.5-20.3),

Prior treatments for RA

Prior treatments for RA are summarized in the table below:

Table 19 - Number (%) of Subjects with Specified Prior Treatment for Rheumatoid Arthritis in Phase 3 Studies

	A3921032 N=399	A3921044 N=797	A3921045 N=610	A3921046 N=792	A3921064 N=717	A3921069 N=952
Prior DMARD treatment criteria	TNFi-IR	MTX-IR	DMARD-IR	DMARD-IR	MTX-IR	MTX-naïve[e]
csDMARDs						
MTX[a]	393 (98.5)	796 (99.9)	518 (84.9)	668 (84.3)	717 (100)	65 (6.8)
Other csDMARDs[b]	123 (30.8)	493 (61.9)	405 (66.4)	791 (99.9)	397 (55.4)	368 (38.7)
bDMARDs						
TNFi[c]	396 (99.2)	127 (15.9)	99 (16.2)	52 (6.6)	51 (7.1)	2 (0.2)
Other bDMARDs[d]	46 (11.5)	37 (4.6)	41 (6.7)	23 (2.9)	15 (2.1)	0

MTX=methotrexate, TNFi=tumour necrosis factor inhibitor, DMARD=disease-modifying anti-rheumatic drug, N=number of subjects treated, bDMARD=biologic DMARD, csDMARD=conventional synthetic DMARD, IR=inadequate responder, CSR=clinical study report.
a. MTX includes MTX and MTX sodium.
b. Other csDMARDs includes actarit, auranofin, aurothioglucose, bucillamine, chloroquine, chloroquine phosphate, gold, hydroxychloroquine, hydroxychloroquine phosphate, hydroxychloroquine sulfate, leflunomide, minocycline, minocycline hydrochloride, penicillamine, sodium aurothiomalate, sulfasalazine, azathioprine, mycophenolate mofetil.
c. TNFi includes adalimumab, certolizumab pegol, etanercept, golimumab, infliximab.
d. Other bDMARDs include abatacept, anakinra, atacicept, baminercept, rituximab, tocilizumab, zanolimumab, canakinumab.
e. ≤ 3 weekly doses of methotrexate.

Inadequate response to prior treatment was based on the investigator's assessment.

Studies A3921032, A3921044, and A3921064 required prior treatment with MTX. Subjects were to have taken oral or parenteral MTX continuously for at least 4 months prior to the first dose of study medication, and be on a stable dose of 7.5 mg to 25 mg weekly for at least 6 weeks prior to the first dose of study medication. In these studies background MTX was used.

In Study A3921046, subjects were required to have had prior treatment with a DMARD, the majority of whom (84.3%) received MTX. Treatment duration and dose stability requirements for permitted DMARDs, including MTX, were similar to those above. In this study, dosing with at least 1 permitted csDMARD continued throughout the course of the study (background DMARD).

Study A3921045 required inadequate response to at least 1 csDMARD or bDMARD. However, a requirement for continuous and stable DMARD dosing prior to the start of study medication was not needed because the DMARD (other than anti-malarial drugs) was washed out and not continued throughout the course of the study (monotherapy).

Prior duration of treatment with MTX and other DMARDs is given in the table below:

Table 20 - Number (%) of Subjects with Specified Duration of Use of Methotrexate and Other csDMARDs in Studies Requiring Inadequate Response to Prior DMARD Treatment

	A3921032	A3921044	A3921045	A3921046	A3921064	Total
With prior MTX	N=399	N=797	N=518	N=742	N=717	N=3173
Unknown duration	3 (<1)	3 (<1)	259 (50)	76 (10)	0	341 (11)
< 4 Months	17 (4)	23 (3)	35 (7)	30 (4)	8 (1)	113 (4)
4-12 Months	77 (19)	236 (30)	69 (13)	156 (21)	255 (36)	793 (25)
>12 Months	302 (76)	535 (67)	155 (30)	480 (65)	454 (63)	1926 (61)
With prior other csDMARDs	--	--	N=83	N=50	--	--
Unknown duration	--	--	20 (24)	0	--	--
< 4 Months	--	--	12 (15)	6 (12)	--	--
4-12 Months	--	--	25 (30)	15 (30)	--	--
>12 Months	--	--	26 (31)	29 (58)	--	--

	A3921032	A3921044	A3921045	A3921046	A3921064	Total

All treatment groups within a study were pooled. Unknown duration implies there is a record of using MTX/DMARDs but there is insufficient date information to calculate a duration.
N=number of subjects with prior treatment, MTX=methotrexate, DMARD=disease-modifying anti-rheumatic drug, csDMARD=conventional synthetic DMARD.

Table 21 - Number (%) of TNFi Treatment Failures and Reason for TNFi Discontinuation Prior to Enrolling in Studies A3921032, A3921045, A3921046, and A3921064

	LOE		Adverse Event		Both AE/LOE		Total	
Study	< 90 Days	≥ 90 Days	< 90 Days	≥ 90 Days	< 90 Days	≥ 90 Days	< 90 Days	≥ 90 Days
A3921032	32 (7)	428 (93)	33 (40)	49 (60)	9 (36)	16 (64)	74 (13)	493 (87)
Other studies[a]	20 (11)	166 (89)	13 (32)	28 (68)	2 (14)	12 (86)	35 (15)	206 (85)
Total	52 (8)	594 (92)	46 (37)	77 (63)	11 (28)	28 (72)	109 (13)	699 (87)

A subject was counted more than once if he or she experienced more than 1 TNFi treatment failure.
AE=adverse event, LOE=lack of efficacy, TNFi=tumour necrosis factor inhibitor.
a. Includes Studies A3921045, A3921046, and A3921064; duration of prior TNFi treatment was not collected in Study A3921044.

Duration of Study Treatment

Table 22 - Median (Range) Duration (Days) of Study Treatment in Phase 3 Studies

	Tofacitinib		Placebo → Tofacitinib		Active Comparator
	5 mg BID	10 mg BID	5 mg BID	10 mg BID	
A3921032	168 (15-218)	168 (3-452[a])	169 (15-192)	168 (6-189)	NA
A3921044 Year 1	446 (2-470)	446 (8-474)	442 (8-462)	444 (1-462)	NA
A3921044 Year 2	709 (2-742)	711 (8-754)	714 (8-736)	714 (1-754)	NA
A3921045	180 (14-202)	180 (12-197)	180 (3-188)	180 (4-196)	NA
A3921046	358 (5-387)	358 (1-376)	361 (21-372)	358 (2-377)	NA
A3921064	363 (7-385)	362 (7-385)	363 (73-368)	363 (1-379)	364 (12-379)[b]
A3921069 Year 1	357 (24-383)	356 (11-378)	NA	NA	353 (9-382)[c]
A3921069 Year 2	716 (1-734)	715 (11-750)	NA	NA	698 (9-737)[c]

BID=twice daily, NA=not applicable, CSR=clinical study report, mg=milligrams.
a. Upper range 452 was due to an incorrect recorded date of 2011 instead of 2010.
b. Adalimumab 40 mg subcutaneously every other week.
c. MTX.

Concomitant DMARD Treatment

Table 23 - Number (%) of Subjects with Concomitant Background DMARD Use in Relevant Phase 3 Studies

	A3921032 N=399	A3921044 N=800	A3921046 N=795	A3921064 N=513
One csDMARD	376 (94.2)	788 (98.5)	537 (67.5)	504 (98.2)
Methotrexate	374 (93.7)	788 (98.5)	407 (51.2)	504 (98.2)
Chloroquine/hydroxychloroquine	2 (0.5)	0	28 (3.5)	0
Leflunomide	0	0	78 (9.8)	0
Sulfasalazine	0	0	23 (2.9)	0
Gold	0	0	1 (0.1)	0
Other	0	0	0	0
Two csDMARDs	21 (5.3)	7 (0.9)	213 (26.8)	3 (0.6)
Three or more csDMARDs	0	1 (0.1)	37 (4.7)	0

Chloroquine/hydroxychloroquine includes hydroxychloroquine, hydroxychloroquine phosphate and hydroxychloroquine sulfate.
Methotrexate includes methotrexate and methotrexate sodium.
Gold includes sodium aurothiomalate, aurothioglucose, auranofin, parenteral gold.
Other includes bucillamine, minocycline hydrochloride, penicillamine.
N=number of subjects randomized, DMARD= disease-modifying anti-rheumatic drug, csDMARD=conventional synthetic DMARD.

The median duration of study treatment for each phase III study was balanced among arms, and is considered adequate to study objectives. The majority of patients were on concomitant treatment with MTX, reflecting the inclusion criteria.

MTX dosing was variable depending on region (i.e. between Japan and Europe). This was considered acceptable, according to the released CHMP scientific advice, provided that appropriate numbers of EU patients dosed with at least 15 mg/week were included in the study.

In the A3921046 study, 27% of subjects were treated with two csDMARDs, in line with inclusion criteria.

Numbers analysed

Table 24 - Number of Subjects by Population in Phase 3 Studies

Table 24 - Number of Subjects by Population in Phase 3 Studies

	A3921032	A3921044[c]	A3921045	A3921046	A3921064	A3921069[c]
Randomized						
Tofacitinib 5 mg BID	133	321	244	318	204	374
Tofacitinib 10 mg BID	134	319	245	318	201	398
Active comparator[d]	--	--	--	--	204	186
Placebo	132	160	122	159	108	--
Total randomized	399	800	611	795	717	958
FAS[a]						
Tofacitinib 5 mg BID	133	316	241	312	201	371
Tofacitinib 10 mg BID	134	309	243	315	199	395
Active comparator[d]	--	--	--	--	201	186
Placebo	132	156	122	158	107	--
Total FAS: n (% of randomized)	399 (100)	781 (97.6)	606 (99.2)	785 (98.7)	708 (98.7)	952 (99.4)
2nd Line Population						
Tofacitinib 5 mg BID	1	281	212	274	201	NA
Tofacitinib 10 mg BID	2	284	209	281	197	NA
Active comparator[d]	--	--	--	--	200	NA
Placebo	0	152	101	139	108	NA
Total 2nd line: n (% of randomized)	3[b] (0.8)	717 (89.6)	522 (85.4)	694 (87.3)	706 (98.5)	NA
3rd Line Population						
Tofacitinib 5 mg BID	132	40	31	41	3	NA
Tofacitinib 10 mg BID	132	32	36	37	4	NA
Active comparator[d]	--	--	--	--	4	NA
Placebo	132	8	21	20	0	NA
Total 3rd line: n (% of randomized)	396 (99.2)	80 (10.0)	88 (14.4)	98 (12.3)	11 (1.5)	NA

FAS=full analysis set, BID=twice daily, mg=milligram, CSR=clinical study report, NA=not applicable, n=number of subjects in population.
a. Primary pre-specified analysis population.
b. 3 subjects in Study A3921032 did not fully meet the 3rd line definition due to lapses in recording prior bDMARD therapy. One subject did not receive a TNFi, but received abatacept.
c. Numbers from Year 1 CSR.
d. Adalimumab in Study A3921064 and methotrexate in Study A3921069.

Outcomes and estimation

A. Studies relevant to structural progression

A.1 A3921044 (background MTX, 2nd line treatment setting MTX-IR):

This was a randomized, 2-year, double-blind, placebo-controlled, parallel group study compared tofacitinib to placebo in the treatment of subjects with active RA who had had an inadequate response to weekly, stable doses of MTX.

Primary analysis at 1 year

The pre-specified primary endpoints were ACR20 response rate at Month 6, mean change from baseline in mTSS change at Month 6, mean change from baseline in HAQ-DI at Month 3, DAS28-4(ESR) <2.6 response rate at Month 6.

The table below summarises the primary efficacy results for study A3921044:

Table 25 – Primary efficacy results for phase 3 clinical studies in rheumatoid arthritis

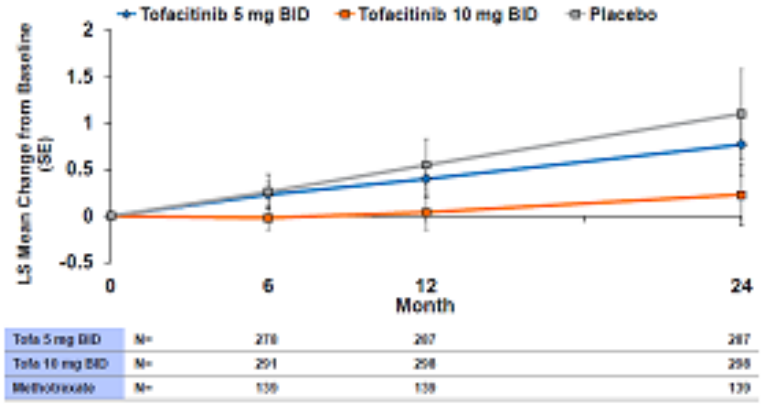
Protocol No. Title	Treatment Groups	No. of Subjects by Treatment Group	Primary Efficacy Results
A3921044 Phase 3 Randomized, Double Blind, Placebo Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 in Patients With Active Rheumatoid Arthritis on Background Methotrexate (1-Year Analysis)	Tofacitinib 5 mg	Assigned to study treatment: 321 Treated: 321 Completed: 0 Ongoing: 250 FAS: 316	Normal Approximation to ACR20 Response Rates at Month 6 (FAS, NRI) Tofa 5 mg BID: n/N (%) 159/309 (51.46); Difference from Placebo 26.13; 95% CI for Difference from Placebo [17.28, 34.97]; p-value <0.0001 Tofa 10 mg BID: 191/309 (61.81); 36.48; [27.73, 45.23]; <0.0001 Placebo: 39/154 (25.32); --; --; --
	Tofacitinib 10 mg	Assigned to study treatment: 319 Treated: 316 Completed: 0 Ongoing: 265 FAS: 309	Summary of LS Mean Changes From Baseline in Modified Total Sharp Scores (mTSS) at Month 6 (FAS, LEP) Tofa 5 mg BID: N 277; LS Mean 0.12; Difference from Placebo -0.34; 95% CI for Difference from Placebo [-0.73, 0.04]; p-value 0.0792 Tofa 10 mg BID: 290; 0.06; -0.40; [-0.79, -0.02]; 0.0376 Placebo: 139; 0.47; --; --; --
	Placebo 5 mg	Assigned to study treatment: 81 Treated: 81 Completed: 0 Ongoing: 64 FAS: 79	Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, Longitudinal Model) Tofa 5 mg BID: N 294; LS Mean -0.40; Difference from Placebo -0.25; 95% CI for Difference from Placebo [-0.34, -0.16]; p-value <0.0001 Tofa 10 mg BID: 300; -0.54; -0.40; [-0.49, -0.31]; <0.0001 Placebo: 146; -0.15; --; --; --
	Placebo 10 mg	Assigned to study treatment: 79 Treated: 79 Completed: 0 Ongoing: 64 FAS: 77	Proportion of Subjects Achieving DAS28-4(ESR) <2.6 at Month 6 (FAS, NRI) Tofa 5 mg BID: n/N (%) 19/265 (7.17); Difference from Placebo 5.61; 95% CI for Difference from Placebo [1.85, 9.38]; p-value 0.0034 Tofa 10 mg BID: 41/257 (15.95); 14.40; [9.44, 19.36]; <0.0001 Placebo: 2/129 (1.55); --; --; --

Year 2 analysis A3921044 Campaign 2

The primary purpose of Campaign 2 was to assess the degree of progression in the tofacitinib treatment arms for 2 years. For these analyses, the Month 12 and Month 24 values for the placebo group (including subjects in both placebo- tofacitinib treatment groups) were extrapolated via LEP from the Month 3 or Month 6 values. Subjects randomised to placebo were advanced to tofacitinib at Month 3 or Month 6 and data beyond advancement were extrapolated.

The mean change from baseline in mTSS (Figure 17) and JSN in the tofacitinib 5 mg and 10 mg b.i.d. groups were lower than placebo at Months 12 and 24; however, unlike the Campaign 1 primary analysis, the difference from placebo at Months 6 and 12 for the 10 mg b.i.d. group was not statistically significant. This difference may be reflective of the overall lower rates of progression in the placebo group in Campaign 2 (Month 6 change from baseline of 0.26); compared to Campaign 1 (Month 6 change from baseline of 0.47). There was minimal change in mean erosion scores in Campaign 2, with similar results seen in the tofacitinib 5 mg b.i.d. and extrapolated placebo groups.

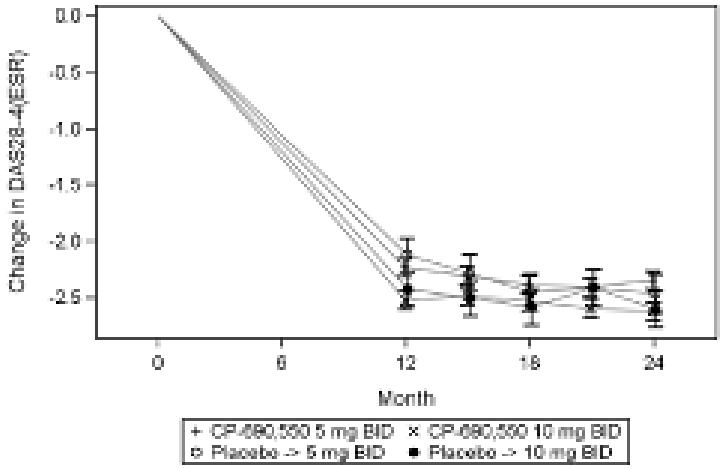
Table 26 – Change from baseline in mTSS at months 6,12 and 24 in study A3921044 Campaign 2 (FAS, LEP)



Source: A3921044 Year 2 CSR Table 14.2.15.1.6.
CSR=clinical study report, BID=twice daily, LEP=linear extrapolation, mg=milligram, FAS=full analysis set, N=number of subjects analysed, tofa=tofacitinib, LS=least squares, SE=standard error, mTSS=modified total Sharp score.

Change from baseline in DAS28-4(ESR) was measured as a secondary endpoint.

Figure 10 – LS mean changes from baseline in DAS28-4(ESR) months 12 through 24 (FAS, longitudinal model, comparisons within sequence)



Source: Table 14.2.13.6

Abbreviations: LS=least squares, BID=twice daily, DAS=Disease Activity Score, ESR=erythrocyte sedimentation rate, FAS=Full Analysis Set, SE=standard error

All treatment groups demonstrated an improvement in DAS28-4(ESR) scores that was sustained to 24 months.

A.2 A3921069 – Monotherapy, MTX naïve, head to head comparison with MTX, 2 years duration

This study was conducted in two phases: a 1 year interim analysis was conducted and the 1 year CSR includes the analysis of all primary endpoints. The Year 2 (end of study) CSR focuses on objectives for the study collected beyond Month 12 and includes an analysis of secondary endpoints beyond Month 12 and a cumulative safety review.

The study was a randomised, 24-month, double-blind, parallel group, active comparator study compared tofacitinib to MTX in the treatment of MTX-naïve subjects with active RA.

Primary analysis at 1 year

The pre-specified primary endpoints were ACR70 response rate and mean change from baseline in mTSS, both analysed at Month 6. A hierarchical analysis of the two endpoints, taking also the two doses into account, was conducted as described previously to control inflation of the type I error.

The table below summarises the primary efficacy outcomes for study A3921069.

Table 27 – Summary of the primary efficacy outcomes for study A3921069

Protocol No. Title	Treatment Groups	No. of Subjects by Treatment Group	Primary Efficacy Results
A3921069 Phase 3 Randomized, Double-Blind Study of the Efficacy and Safety of 2 Doses of CP-690,550 Compared to Methotrexate in Methotrexate-Naïve Patients With Rheumatoid Arthritis (1-Year Analysis)	Tofacitinib 5 mg	Assigned to study treatment: 374 Treated: 371 Completed: 0 Ongoing: 307 FAS: 371	Normal Approximation to ACR70 Response Rates at Month 6 (FAS, NRI) Tofa 5 mg BID: 94/369 (25.47); Difference from MTX: 13.51; 95% CI for Difference from MTX: [7.05, 19.97]; p-value: <0.0001 Tofa 10 mg BID: 148/393 (37.66); Difference from MTX: 25.70; 95% CI for Difference from MTX: [18.99, 32.40]; p-value: <0.0001 MTX: 22/184 (11.96); Difference from MTX: --; 95% CI for Difference from MTX: --; p-value: -- Summary of LS Mean Changes From Baseline in Modified Total Sharp Scores (mTSS) at Month 6 (FAS, LEP) Tofa 5 mg BID: N: 346; LS Mean: 0.18; Difference from MTX: -0.66; 95% CI for Difference from MTX: [-1.03, -0.28]; p-value: 0.0006 Tofa 10 mg BID: N: 369; LS Mean: 0.04; Difference from MTX: -0.81; 95% CI for Difference from MTX: [-1.18, -0.44]; p-value: <0.0001 MTX: N: 166; LS Mean: 0.84; Difference from MTX: --; 95% CI for Difference from MTX: --; p-value: --
	Tofacitinib 10 mg	Assigned to study treatment: 398 Treated: 395 Completed: 0 Ongoing: 328 FAS: 395	
	Methotrexate 10 to 20 mg/week	Assigned to study treatment: 186 Treated: 186 Completed: 0 Ongoing: 134 FAS: 186	

Source: A3921032 CSR Tables 14.1.1.1, 14.2.3.1.1, 14.2.13.3.1, 14.2.15.10.1; A3921044 1 year Report CSR Tables 14.1.1.1.2, 14.2.1.1, 14.2.11.5, 14.2.15.1.6, 14.2.13.19; A3921045 CSR Tables 14.1.1.1, 14.2.1.1, 14.2.1.2, 14.2.15.10.1; A3921046 CSR Tables 14.1.1.1.2, 14.2.1.1, 14.2.11.1.7, 14.2.13.4.1; A3921064 CSR Tables 14.1.1.1.2, 14.2.1.1, 14.2.11.5, 14.2.13.11.1; A3921069 1 year Report CSR Tables 14.1.1.1, 14.2.3.1, 14.2.15.1.6.

ACR20(70)=American College of Rheumatology 20% (70%) improvement, BID=twice daily, CI=confidence interval, DAS28=disease activity score 28 joints, DMARD=disease modifying anti-rheumatic drug, ESR=erythrocyte sedimentation rate, FAS=full analysis set, HAQ-DI=Health Assessment Questionnaire-Disability Index, LEP=linear extrapolation, LS mean=least squares mean, mTSS=modified total Sharp score, N=number of subjects, n=number of subjects meeting specified criteria, NRI=non-responder imputation, QOW=every other week, SC=subcutaneous, TNF=tumor necrosis factor, Tofa=tofacitinib, Ada=adalimumab, MTX=methotrexate, No=number, mg=milligram, CSR=clinical study report

Secondary endpoints:

Rates of non-radiographic progression (1 year analysis)

Numbers of patients who showed lack of radiographic progression (defined as change from baseline in mTSS of ≤ 0.5 units) was a secondary endpoint.

Both tofacitinib groups showed significantly better rates of no radiographic progression compared to the MTX group at 6 and 12 months. (p≤0.0013).

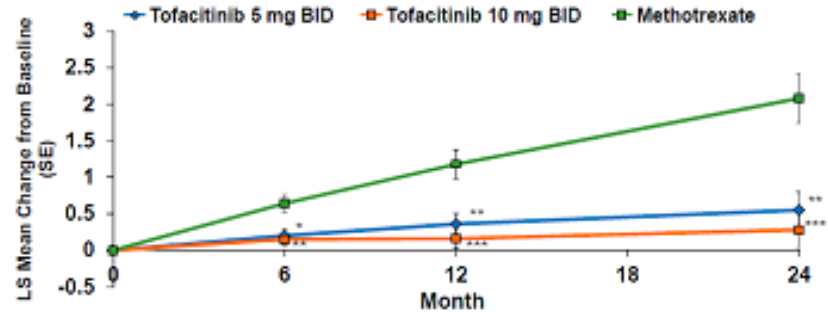
2 year analysis A3921069 (Campaign 2)

Structure preservation:

As with Study A3921044, all hand and foot radiographs for all subjects were re-assessed at each time point (baseline, Month 3 if done, and Months 6, 12, and 24) by readers blinded to treatment group and sequence of radiograph acquisition. However, unlike the placebo comparator in Study A3921044, the MTX comparator group in Study A3921069 remained intact throughout the course of the study, thereby allowing comparison of a dataset containing a higher proportion of observed (non-extrapolated) data throughout the entire course of the study.

The changes from baseline in mTSS at Months 6, 12, and 24 for the 3 treatment groups in Study A3921069 are shown in Figure 11. A continued increase in change from baseline in mTSS was observed in the MTX group through 24 months of treatment, whereas consistently smaller increases were observed for both tofacitinib treatment groups. Statistically significant differences from MTX were observed for both tofacitinib 5 and 10 mg b.i.d. at each time point, including Month 24.

Figure 11 – Change from baseline in mTSS at months 6, 12 and 24 for tofacitinib and methotrexate in study A3921069 Campaign 2 (FAS, LEP)



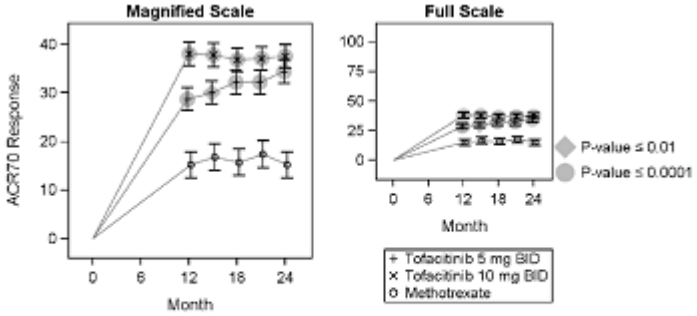
Tofa 5 mg BID	N=	348	347	348
Tofa 10 mg BID	N=	372	373	373
Methotrexate	N=	167	171	171

* p ≤0.05, **p <0.001, ***p <0.0001 versus methotrexate.
Source: A3921069 Year 2 CSR Table 14.2.15.1.6.
mg=milligram, BID=twice daily, FAS=full analysis set, LS=least squares, mTSS=modified total Sharp score, SE=standard error, CSR=clinical study report, LEP=linear extrapolation, N=number of subjects analysed, tofa=tofacitinib.

Rates of non-radiographic progression and ACR70 response rate were measured through to Month 24

No progression in mTSS was defined as change from baseline ≤ 0.5 units.

Figure 12 – ACR70 response rates (%) (FAS, NRI, 2 year analysis)



Source: Table 14.2.3.1

Abbreviations: ACR70 = American College of Rheumatology's (ACR) definition for calculating improvement in RA; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures, NRI = nonresponder imputation, FAS = full analysis set

Table 27 – Normal approximation of rates (%) of patients with no progression in mTSS at months 12 and 24 (FAS, LEP, comparisons to MTX, 2 year analysis)

Time point/ Treatment	N	n	%	Difference From MTX			
				Difference in %	95% CI for Difference Lower	Upper	p-value
Month 12							
Tofacitinib 5 mg BID	347	286	82.42	13.41	5.40	21.42	0.0010
Tofacitinib 10 mg BID	373	327	87.67	18.66	10.96	26.35	<0.0001
Methotrexate	171	118	69.01				
Month 24							
Tofacitinib 5 mg BID	348	278	79.89	14.97	6.67	23.27	0.0004
Tofacitinib 10 mg BID	373	312	83.65	18.73	10.65	26.81	<0.0001
Methotrexate	171	111	64.91				

Source: Table 14.2.15.4.1, 16.2.6.13
If patient did not have any valid postbaseline radiographs, they were not included in this summary.
No progression in mTSS was defined as a change from Baseline ≤0.5 units.
Abbreviations: BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, LEP = linear extrapolation, mTSS = modified Total Sharp Score, MTX = methotrexate

The superior benefit of tofacitinib as monotherapy compared to MTX on structural preservation is maintained through to 24 months (difference in mean change from baseline mTSS p=0.0004 for tofactinib 5 mg b.i.d. compared with MTX). 79.89% of tofacitinib 5 mg b.i.d. treated patients continue to demonstrate no evidence of radiographic progression from baseline at 24 months, compared with 64.91% of MTX treated patients.

ACR70 response rate was also sustained through to month 24 and the 5 mg b.i.d. tofacitinib group showed further improvement beyond month 12 to in excess of 30% ACR70 response rate at month 24.

There is a clear difference in structural preservation results from the two Phase III studies that addressed this. In Study A3921069, tofacitinib at daily doses of both 5 mg and 10 mg b.i.d. demonstrated clear superiority over MTX in slowing of structural progression by 6 months that was maintained at 12 and 24 months. The level of statistical significance was compelling (p<0.001 for tofacitinib 5 mg b.i.d. compared with MTX at 24 months) and ~80% of patients in the tofacitinib 5 mg b.i.d. group compared with ~65% in the MTX group showing no evidence of radiographic progression from baseline. ACR70 response rates were also statistically significantly better for tofacitinib 5 mg b.i.d. compared with MTX at 6 months and the ACR70 response rate continued to improve beyond month 12 to in excess of 30% at Month 24.

A. Studies relevant to 2nd line treatment setting (signs, symptoms and physical function)

B.1 Study A3921045 Monotherapy tofacitinib in 2nd line treatment setting

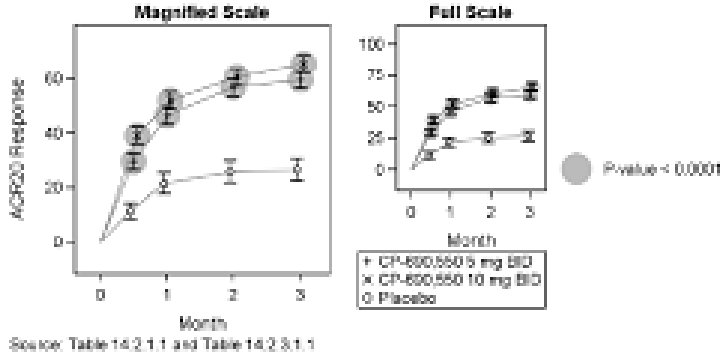
The pre-specified primary endpoints, all analysed at 3 months, were ACR20 response rate, mean change from baseline in HAQ-DI and DAS28-4(ESR) <2.6 response rate. The endpoints were analysed in accordance with the step-down hierarchy as described previously to control inflation of the type I error.

The tables and figures below summarises the primary efficacy outcomes for study A3921045.

Table 28 – Primary efficacy results for phase 3 clinical studies in rheumatoid arthritis

Protocol No. Title	Treatment Groups	No. of Subjects by Treatment Group	Primary Efficacy Results
A3921045 Phase 3, Randomized, Double Blind, Placebo Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 Monotherapy in Patients with Active Rheumatoid Arthritis	Tofacitinib 5 mg	Assigned to study treatment: 244 Treated: 243 Completed: 232 FAS: 241	Normal Approximation to ACR20 Response Rates at Month 3 (FAS, NRI) Tofa 5 mg BID: n/N (%) 144/241 (59.75); Difference from Placebo 33.08; 95% CI for Difference from Placebo [23.04, 43.13]; p-value <0.0001 Tofa 10 mg BID: 159/242 (65.70); 39.04; [29.12, 48.95]; <0.0001 Placebo: 32/120 (26.67); --; --; --
	Tofacitinib 10 mg	Assigned to study treatment: 245 Treated: 245 Completed: 218 FAS: 243	Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, Longitudinal Model) Tofa 5 mg BID: N 237; LS Mean -0.50; Difference from Placebo -0.31; 95% CI for Difference from Placebo [-0.43, -0.20]; p-value <0.0001 Tofa 10 mg BID: 227; -0.57; -0.38; [-0.50, -0.27]; <0.0001 Placebo: 109; -0.19; --; --; --
	Placebo 5 mg	Assigned to study treatment: 61 Treated: 61 Completed: 54 FAS: 61	
	Placebo 10 mg	Assigned to study treatment: 61 Treated: 61 Completed: 51 FAS: 61	Proportion of Subjects Achieving DAS28-4(ESR) <2.6 at Month 3 (FAS, NRI) Tofa 5 mg BID: n/N (%) 13/232 (5.60); Difference from Placebo 1.22; 95% CI for Difference from Placebo [-3.57, 6.00]; p-value 0.6179 Tofa 10 mg BID: 20/229 (8.73); 4.35; [-0.90, 9.59]; 0.1042 Placebo: 5/114 (4.39); --; --; --

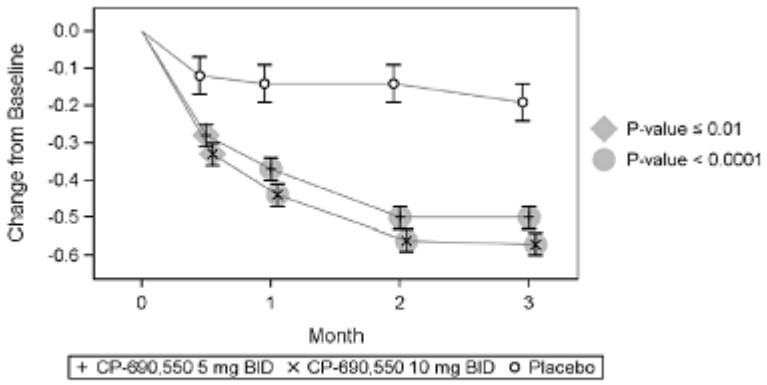
Figure 13 - ACR20 response rate through to 3 months



Source: Table 14.2.1.1 and Table 14.2.3.1.1

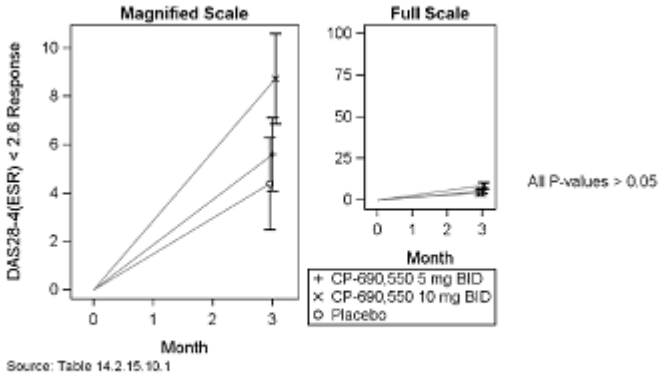
Abbreviations: ACR20 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures; BID = twice daily; FAS = full analysis set; NRI = nonresponder imputation; SE = standard error

Table 29 - Mean change from baseline in HAQ-DI through to 3 months



Source: Table 14.2.13.3.1

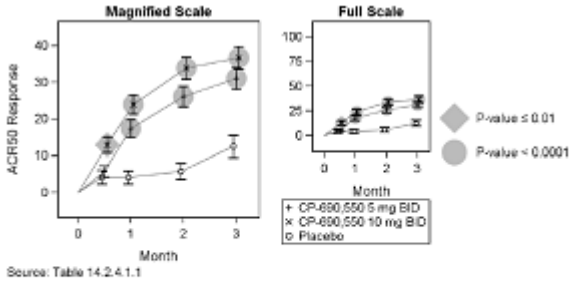
Figure 14 - DAS28-4(ESR) <2.6 response rate (induction of "remission")



Source: Table 14.2.15.10.1

Abbreviations: BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, NRI = nonresponder imputation, SE= standard error

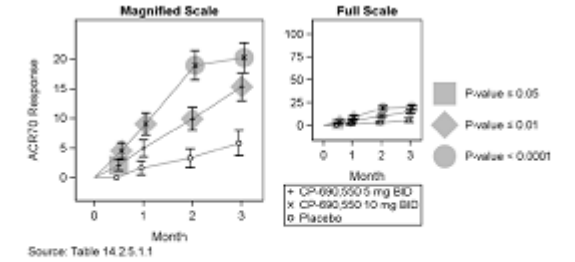
Figure 15 - ACR50 response rate (secondary endpoint)



Source: Table 14.2.4.1.1

Abbreviations: ACR50 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, FAS = full analysis set, NRI = nonresponder imputation, SE = standard error

Figure 16 - ACR70 response rate (secondary endpoint)



Source: Table 14.2.5.1.1

Abbreviations: ACR70 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, FAS = full analysis set, NRI = nonresponder imputation, SE = standard error

B.2 Study A3921064. Tofacitinib in combination with background MTX in 2nd line setting. Adalimumab active comparator arm (secondary objective)

This randomized, 1-year, double-blind, placebo-controlled, parallel group study compared tofacitinib and adalimumab to placebo in the treatment of subjects with active RA who had had an inadequate response to weekly, stable doses of MTX, had not had an inadequate response to any TNFi, and were naïve to adalimumab.

The table below summarises the primary efficacy outcomes for study A3921064**.**

The pre-specified primary endpoints, were ACR20 response rate at month 6, mean change from baseline in HAQ-DI at month 3 and DAS28-4(ESR) <2.6 response rate at month 6. The endpoints were analysed in accordance with the step-down hierarchy as described previously to control inflation of the type I error.

Table 29 – Primary efficacy results for phase 3 clinical studies in rheumatoid arthritis

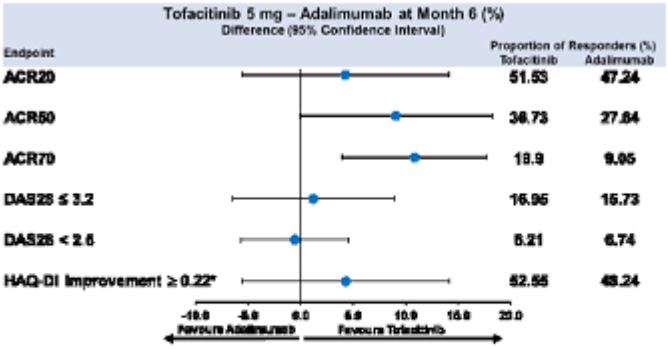
Protocol No. Title	Treatment Groups	No. of Subjects by Treatment Group	Primary Efficacy Results
A3921064 Phase 3 Randomized, Double-Blind, Active Comparator, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 in Patients with Active Rheumatoid Arthritis on Background Methotrexate	Tofacitinib 5 mg	Assigned to study treatment: 204 Treated: 204 Completed: 150 FAS: 201	Normal Approximation to ACR20 Response Rates at Month 6 (FAS, NRI) n/N (%) / Difference from Placebo / 95% CI for Difference from Placebo / p-value Tofa 5 mg BID: 101/196 (51.53) / 23.22 / [12.16, 34.29] / <0.0001 Tofa 10 mg BID: 103/196 (52.55) / 24.24 / [13.18, 35.31] / <0.0001 Ada 40mg SC QOW: 94/199 (47.24) / 18.93 / [7.90, 29.96] / 0.0007 Placebo: 30/106 (28.30) / -- / -- / -- Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, Longitudinal Model) N / LS Mean / Difference from Placebo / 95% CI for Difference from Placebo / p-value Tofa 5 mg BID: 188 / -0.55 / -0.31 / [-0.43, -0.19] / <0.0001 Tofa 10 mg BID: 185 / -0.61 / -0.38 / [-0.50, -0.25] / <0.0001 Ada 40mg SC QOW: 190 / -0.49 / -0.25 / [-0.37, -0.13] / <0.0001 Placebo: 98 / -0.24 / -- / -- / -- Proportion of Subjects Achieving DAS28-4(ESR) <2.6 at Month 6 (FAS, NRI) n/N (%) / Difference from Placebo / 95% CI for Difference from Placebo / p-value Tofa 5 mg BID: 11/177 (6.21) / 5.12 / [0.98, 9.26] / 0.0151 Tofa 10 mg BID: 22/176 (12.50) / 11.41 / [6.08, 16.73] / <0.0001 Ada 40mg SC QOW: 12/178 (6.74) / 5.65 / [1.40, 9.90] / 0.0091 Placebo: 1/92 (1.09) / -- / -- / --
	Tofacitinib 10 mg	Assigned to study treatment: 201 Treated: 201 Completed: 158 FAS: 199	
	Placebo 5 mg	Assigned to study treatment: 56 Treated: 56 Completed: 47 FAS: 56	
	Placebo 10 mg	Assigned to study treatment: 52 Treated: 52 Completed: 39 FAS: 51	
	Adalimumab 40 mg SC injection QOW	Assigned to study treatment: 204 Treated: 204 Completed: 162 FAS: 201	

Secondary objective: comparison with adalimumab

Study A3921064 incorporated an active comparator arm, the TNFi adalimumab at 40 mg SC QOW, which was compared with tofacitinib as a secondary objective. The study was not designed or powered to formally test a superiority or non-inferiority hypothesis for tofacitinib efficacy compared to adalimumab.

Figure 17 compares results across selected primary and secondary efficacy endpoints and shows the differences (tofacitinib 5 mg b.i.d. minus adalimumab) in the proportion of subjects achieving these efficacy endpoints. Point estimates to the left of the vertical line favour adalimumab while those to the right favour tofacitinib.

Figure 17 – Efficacy of tofacitinib 5mg BID compared to adalimumab in phase 3 study A3921064



*Time points are Month 3 for HAQ-DI and Month 6 for the remaining variables.
Source: A3921064 CSR Tables 14.2.1.1, 14.2.2.1, 14.2.3.1, 14.2.13.10.1, 14.2.13.11.1, 14.2.11.8.3.
ACR20(50, 70)=American College of Rheumatology ≥20% (≥50%, ≥70%) improvement, BID=twice daily, DAS28=disease activity score 28 joints, HAQ-DI=health assessment questionnaire disability index, CSR=clinical study report, FAS=full analysis set, NRI=non-responder imputation, mg=milligrams.

B.3 Study A3921046. 2nd line treatment setting. Background csDMARD.

This randomised, 1-year, double-blind, placebo-controlled, parallel group study compared tofacitinib to placebo in the treatment of subjects with active RA who had had an inadequate response to at least 1 DMARD.

The pre-specified primary endpoints, were ACR20 response rate at month 6, mean change from baseline in HAQ-DI at month 3 and DAS28-4(ESR) <2.6 response rate at month 6. The endpoints were analysed in accordance with the step-down hierarchy as described previously to control inflation of the type I error.

The table below summarises the primary efficacy results for study A3921046.

Table 30 – Primary efficacy results for Phase 3 clinical studies in rheumatoid arthritis

Protocol No. Title	Treatment Groups	No. of Subjects by Treatment Group	Primary Efficacy Results
A3921046 Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of CP-690,550 in Patients with Active Rheumatoid Arthritis on Background DMARDs	Tofacitinib 5 mg	Assigned to study treatment: 318 Treated: 315 Completed: 261 FAS: 312	Normal Approximation to ACR20 Response Rates at Month 6 (FAS, NRI) Tofa 5 mg BID: n/N (%) 164/311 (52.73); Difference from Placebo 21.52; 95% CI for Difference from Placebo [12.39, 30.65]; p-value <0.0001 Tofa 10 mg BID: 180/309 (58.25); 27.04; [17.94, 36.13]; <0.0001 Placebo: 49/157 (31.21); --; --; --
	Tofacitinib 10 mg	Assigned to study treatment: 318 Treated: 318 Completed: 252 FAS: 315	Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, Longitudinal Model) Tofa 5 mg BID: N 292; LS Mean -0.46; Difference from Placebo -0.26; 95% CI for Difference from Placebo [-0.35, -0.16]; p-value <0.0001 Tofa 10 mg BID: 292; -0.56; -0.35; [-0.44, -0.26]; <0.0001 Placebo: 147; -0.21; --; --; --
	Placebo 5 mg	Assigned to study treatment: 79 Treated: 79 Completed: 71 FAS: 79	
	Placebo 10 mg	Assigned to study treatment: 80 Treated: 80 Completed: 67 FAS: 79	Proportion of Subjects Achieving DAS28-4(ESR) <2.6 at Month 6 (FAS, NRI) Tofa 5 mg BID: n/N (%) 24/263 (9.13); Difference from Placebo 6.42; 95% CI for Difference from Placebo [2.07, 10.77]; p-value 0.0038 Tofa 10 mg BID: 36/270 (13.33); 10.63; [5.80, 15.45]; <0.0001 Placebo: 4/148 (2.70); --; --; --

A. Study relevant to 3rd line setting

C.1 Study A3921032. Background MTX. TNFi-IR patients.

This randomised, 6-month, double-blind, placebo-controlled, parallel group study compared tofacitinib to placebo in the treatment of subjects with active RA who had had an inadequate response to a TNFi.

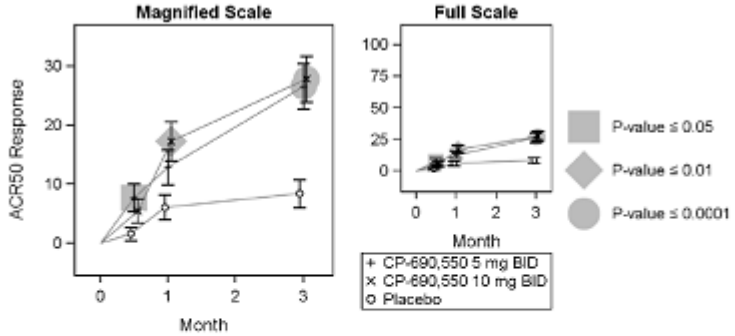
The pre-specified primary endpoints, were ACR20 response rate at month 3, mean change from baseline in HAQ-DI at month 3 and DAS28-4(ESR) <2.6 response rate at month 3. The endpoints were analysed in accordance with the step-down hierarchy as described previously to control inflation of the type I error.

The table below displays primary efficacy results for study A3921032.

Table 31 – Primary efficacy results for phase 3 clinical studies in rheumatoid arthritis

Protocol No. Title	Treatment Groups	No. of Subjects by Treatment Group	Primary Efficacy Results
A3921032 Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of CP-690,550 in Patients With Active Rheumatoid Arthritis on Background Methotrexate With Inadequate Response to TNF Inhibitors	Tofacitinib 5 mg BID	Assigned to study treatment: 133 Treated: 133 Completed: 107 FAS: 133	Normal Approximation to ACR20 Response Rates at Month 3 (FAS, NRI) Tofa 5 mg BID: n/N (%) 55/132 (41.67); Difference from Placebo 17.23; 95% CI for Difference from Placebo [6.06, 28.41]; p-value 0.0024 Tofa 10 mg BID: 64/133 (48.12); 23.69; [12.45, 34.92]; <0.0001 Placebo: 32/131 (24.43); --; --; --
	Tofacitinib 10 mg BID	Assigned to study treatment: 134 Treated: 134 Completed: 103 FAS: 134	
	Placebo 5 mg	Assigned to study treatment: 66 Treated: 66 Completed: 53 FAS: 66	Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, Longitudinal Model) Tofa 5 mg BID: N 117; LS Mean -0.43; Difference from Placebo -0.25; 95% CI for Difference from Placebo [-0.36, -0.15]; p-value <0.0001 Tofa 10 mg BID: 125; -0.46; -0.28; [-0.38, -0.17]; <0.0001 Placebo: 118; -0.18; --; --; --
	Placebo 10 mg	Assigned to study treatment: 66 Treated: 66 Completed: 48 FAS: 66	Proportion of Subjects Achieving DAS28-4(ESR) <2.6 at Month 3 (FAS, NRI) Tofa 5 mg BID: n/N (%) 8/119 (6.72); Difference from Placebo 5.05; 95% CI for Difference from Placebo [0.00, 10.10]; p-value 0.0496 Tofa 10 mg BID: 11/125 (8.80); 7.13; [1.66, 12.60]; 0.0105 Placebo: 2/120 (1.67); --; --; --

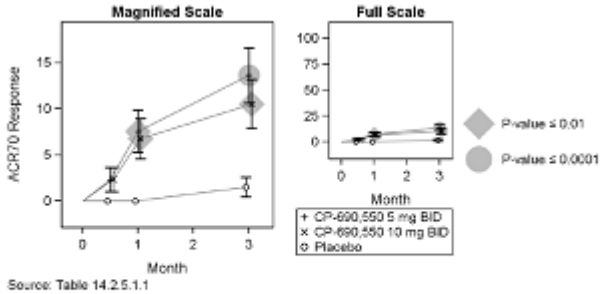
Figure 18 – ACR50 response rate through month 3



Source: Table 14.2.4.1.1

Abbreviations: ACR50 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥50% improvement in tender and swollen joint counts and ≥50% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, FAS = full analysis set, NRI = nonresponder imputation, SE = standard error

Figure 19 – ACR70 response rate through month 3



Source: Table 14.2.5.1.1

Abbreviations: ACR70 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥70% improvement in tender and swollen joint counts and ≥70% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, FAS = full analysis set, NRI = nonresponder imputation, SE = standard error

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30 - Summary of efficacy for trial A3921044

Title: Phase 3 Randomized, 2 years, Double Blind, Placebo Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 in Patients With Active Rheumatoid Arthritis on Background Methotrexate (1-Year Analysis)					
Study identifier	**A3921044**				
Design	Study 1044 was a phase 3, randomized, 2-year, double-blind, placebo-controlled, parallel group study of efficacy and safety data of 5 mg and 10 mg doses of CP in patients with active RA on background MTX. 750 Patients were randomized in a 4:4:1:1 ratio to 1 of 4 treatment groups (CP 5 mg BID, CP 10 mg BID, placebo to CP 5 mg BID, placebo to CP 10 mg BID. The study duration was 2 years, divided in 2 periods (DB, PC period of 3 to 6 months and DB extension period of 18 months).Only analyses through month 12 are reported since the study is still ongoing.				
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		3 to 6 months DB, PC period 6 to 24 months DB active extension period		
Hypothesis	Superiority versus placebo				
Treatments groups	CP-690,550 5 mg BID (sequence 1)		321, 12 month		
	CP-690,550 10 mg BID (sequence 2)		319, 12 months		
	placebo →CP-690,550 5 mg (sequence 3)		81, 3 to 6 months		
	placebo →CP-690,550 10 mg (sequence 4)		79, 3 to 6 months		
Endpoints and definitions	Co-primary endpoints	**ACR20 at month 6**			
		mTSS at month 6			
		HAQ-DI at month 3			
		DAS28-4(ESR) <2.6 at month 6			
Database lock	<date>				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	**Full analysis set (FAS)**				
Descriptive statistics and estimate variability	Treatment group		**placebo**	**CP-690,550 5 mg BID**	**CP-690,550 10 mg BID**
	Number of subject		154	309	309
	ACR20 at month 6		25.32%	51.16%	61.81%
	Number of subject		139	277	290
	mTSS at month 6		LS mean 0.47	LS mean 0.12	LS mean 0.06

	Number of subject	146	294	300
	HAQ-DI at month 3	LS mean -0.15	LS mean -0.40	LS mean -0.54
	Number of subject	129	265	257
	DAS28-4(ESR) <2.6 at month 6	1.55%	7.17%	18.29%

Effect estimate per comparison	**ACR20 at month 6**	**Comparison with placebo**	**CP-690,550 5 mg BID**	**CP-690,550 10 mg BID**
		Difference versus placebo	26.13%	36.48%
		95%CI for difference	17.28, 34.97	27.73, 45.23
		P-value	<0.0001	<0.0001
	mTSS at month 6	Difference versus placebo	-0.34	-0.40
		95%CI for difference	-0.73, 0.04	-0.49, -0.02
		P-value	**0.0792**	0.0376
	HAQ-DI at month 3	Difference versus placebo	-0.25	-0.40
		95%CI for difference	-0.34, -0.16	-0.49, -0.31
		P-value	<0.0001	<0.0001
	DAS28-4(ESR) <2.6 at month 6	Difference versus placebo	5.61	16.73
		95%CI for difference	1.85, 9.38	11.55, 21.92
		P-value	0.0034	<0.0001
Notes	N= number of patients			
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >**			

Table 31 - Summary of efficacy for trial A3921069 (1 year analysis)

Title: Phase 3 Randomized, Double Blind, Active Comparator Study of the Efficacy and Safety of 2 Doses of CP-690,550 Compared to Methotrexate in Methotrexate Naïve Patients with Rheumatoid Arthritis (1-Year Analysis)		
Study identifier	**A3921069**	
Design	Study 1069 was a phase 3, randomized, 2-year, double-blind, active comparator, parallel group study of efficacy and safety data of 5 mg and 10 mg doses of CP compared with MTX 10 – 20 mg /week in patients with active RA 958 Patients were randomized in a 2:2:1 ratio to 1 of 3 treatment groups (CP 5 mg BID, CP 10 mg BID, MTX 10 – 20 mg/wk. The study duration was 2 years, DB with active comparator throughout. Co-primary endpoints at 6 months. I year analysis.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months 6 to 24 months
Hypothesis	Superiority versus MTX	
Treatments groups	CP-690,550 5 mg BID	374
	CP-690,550 10 mg BID	398

	Methotrexate 10 – 20 mg/wk		186
Endpoints and definitions	Co-primary endpoints	**ACR70 at month 6**	
		mTSS at month 6	
Database lock	<date>		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	**Full analysis set (FAS)**			
Descriptive statistics and estimate variability	Treatment group	**Methotrexate**	**CP-690,550 5 mg BID**	**CP-690,550 10 mg BID**
	Number of subject	184	369	393
	ACR70 at month 6	11.96%	25.47%	37.66%
	Number of subject	166	346	369
	mTSS at month 6	LS mean 0.84	LS mean 0.8	LS mean 0.04

Effect estimate per comparison	**ACR70 at month 6**	**Comparison with MTX**	**CP-690,550 5 mg BID**	**CP-690,550 10 mg BID**
		Difference versus MTX	13.51%	25.70%
		95%CI for difference	7.05,19.97	18.99,32.40
		P-value	<0.0001	<0.0001
	mTSS at month 6	Difference versus MTX	-0.66	-0.81
		95%CI for difference	-1.03,-0.28	-1.18, -0.44
		P-value	0.0006	<0.0001
Notes	N= number of patients			
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >**			

Table 32 - Summary of efficacy for trial A3921045

Title: Phase 3, Randomized, Double Blind, Placebo Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 monotherapy in Patients with Active Rheumatoid Arthritis		
Study identifier	**A3921045**	
Design	Phase 3, randomized, 6-month, double-blind, placebo-controlled, 954 patients randomized in 4 parallel-groups study. Following 3 months of treatment, patients who were randomized to first administered placebo began receiving CP-690,550 in a blinded fashion at either 5 mg or 10 mg for the remainder of the 6-month study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	3 month <time> <not applicable> <time> <not applicable>
Hypothesis	Superiority	
Treatments groups	CP-690,550 5 mg BID (sequence 1)	N= 244, 6 month duration
	CP-690,550 10 mg BID (sequence 2)	N= 245, 6 month duration

	placebo →CP-690,550 5 mg (sequence 3)		N=61, 3 month
	placebo →CP-690,550 10 mg (sequence 4)		N=61, 3 month
Endpoints and definitions	**Primary endpoint**	ACR 20 at month 3	
	Primary endpoint	Change from baseline HAQ-DI at month 3	
	Primary endpoint	DAS28-4 (ESR) < 2.6 at month 3	
Database lock	<date>		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	**Full analysis set (FAS)** : all patients who were randomized to study and received at least 1 dose of study drug at month 3			
Descriptive statistics and estimate variability	Treatment group	placebo	CP-690,550 5 mg BID	CP-690,550 10 mg BID
	Number of subject	120	241	242
	ACR 20 at month 3	**26.67%**	**59.75%**	**65.70%**
	Number of subject	109	237	227
	Change from baseline HAQ-DI at month 3	LS mean -0.19	LS mean -0.50	LS mean -0.57
	Number of subject	104	229	219
	DAS28-4 (ESR) < 2.6 at month 3	4.81%	6.11%	10.05%

Effect estimate per comparison	**ACR 20 at month 3**	Comparison with placebo	CP-690,550 5 mg BID	CP-690,550 10 mg BID
		Difference versus placebo	33.08	39.04
		95% CI for difference	23.04, 43.13	29.12, 48.95
		P-value	<0.0001	<0.0001
	Change from baseline HAQ-DI at month 3	Comparison with placebo	CP-690,550 5 mg BID	CP-690,550 10 mg BID
		Difference versus placebo	-0.31	-0.38
		95% CI for difference	-0.43, -0.20	-0.50, -0.27
		P-value	<0.0001	<0.0001
	DAS28-4 (ESR) < 2.6 at month 3	Difference versus placebo	CP-690,550 5 mg BID	CP-690,550 10 mg BID

		95% CI for difference	1.31	5.24
		95% CI for difference	-3.85, 6.46	-0.49, 10,96
		P-value	0.6193	0.0728
Notes	<free text>			
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >**			

Table 33 - Summary of efficacy for trial A3921064

Title: Phase 3 Randomized, Double-Blind, Active Comparator, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of CP-690,550 in Patients with Active Rheumatoid Arthritis on Background Methotrexate			
Study identifier	A3921064		
Design	Phase 3, randomized, one year, placebo-controlled, with adalimumab as active comparator, 5 parallel treatment sequences. At month 3, if a patient was randomized to active treatment (Treatment Sequences 1, 2, or 5) and considered as non responder, that patient was to remain on the same treatment, at the same dose, for the duration of the study. If a nonresponder patient was randomized to treatment sequences 3 or 4, he switched to the second predetermined treatment in a blinded manner. At the end of month 6, all patients were automatically advanced to their second predetermined treatment in a blinded fashion for the remainder of the study.		
	Duration of main phase: Duration of Extension phase:		3 to 6 months in DB (end of PC phase) 6 months in DB extension period
Hypothesis	This protocol is designed to establish the superiority of two doses (5 and 10 mg BID) ofCP-690,550 to placebo for all three primary endpoints		
Treatments groups	CP-690,550 5 mg BID (sequence 1)		N=204, 12 months
	CP-690,550 10 mg BID (sequence2)		N=201, 12 months
	Placebo (sequence3)		N=56, 6 months (only 3 months for a non responder patient)
	Placebo (sequence4)		N=52, 6 months (only 3 months for a non responder patient)
	Adalimumab 40 mg q2w (sequence 5)		N= 204, 12 months
Endpoints and definitions	**Primary endpoint**	ACR 20 at month 6	≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures
	Primary endpoint	HAQ-DI change at month 3	
	Primary endpoint	DAS28-4 (ESR) <2.6 at month 6	
Database lock	<date>		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Full Analysis Set (FAS):** all patients who were randomized to the study and received at least 1 dose of the study drug (CP690,550), adalimumab or placebo.		

Descriptive statistics and estimate variability	Treatment group	CP-690,550 5 mg BID	CP-690,550 10 mg BID	adalimumab	placebo→CP 5 or 10 mg
	Number of subject FAS	201	199	201	107
	ACR 20 responder rate at month 6	51.53% (N=196)	52.55% (N=196)	47.24% (N=196)	28.30% (N=106)
	HAQ-DI change at month 3 (LS mean)	-0.55 (N=188)	-0.61 (N=185)	-0.49 (N=190)	-0.24 (N=90)
	DAS28-4 (ESR) <2.6 at month 6	7.34 % (N=177)	12.50% (N=176)	6.18% (N=178)	1.09% (N=92)

Effect estimate per comparison	**ACR 20 responder rate at month 6**	**Comparison with placebo**	**CP-5 mg BID**	**CP-10 mg BID**	**ADA**
		Difference versus placebo	23.22	24.24	18.93
		95% CI for difference	12.16, 34.29	13.18, 35.31	7.90, 29.96
		P-value	<0.0001	<0.0001	0.0007
	HAQ-DI change at month 3 (LS mean)	**Comparison with placebo**	**CP-5 mg BID**	**CP-10 mg BID**	**ADA**
		Difference versus placebo	-0.31	-0.38	-0.25
		95% CI for difference	-0.43, -0.19	-0.50, -0.25	-0.37, -0.13
		P-value	<0.0001	<0.0001	<0.0001
	DAS28-4 (ESR) <2.6 at month 6	**Comparison with placebo**	**CP-5 mg BID**	**CP-10 mg BID**	**ADA**
		Difference versus placebo	6.25	11.41	5.09
		95% CI for difference	1.86, 10.64	6.08, 16.73	0.96, 9.21
		P-value	0.0051	<0.0001	0.0154
Notes	N = number of analysed patients (different from number of patients meeting prespecified criteria) **There are discrepancies in the number of patients in the overall FAS population and with analysed patients for each endpoint**				
Analysis description	**Secondary analysis : comparison with adalimumab**				

	ACR 20 responder rate at month 6	**Comparison with ADA**	**CP-5 mg BID**	**CP-10 mg BID**
		Difference versus ADA	4.29	5.31
		95% CI for difference	-5055, 14014	-4.56, 15.16
		P-value	0.3929	0.2901
	HAQ-DI change at month 3 (LS mean)	**Comparison with ADA**	**CP-5 mg BID**	**CP-10 mg BID**
		Difference versus ADA	-0.06	-0.12
		95% CI for difference	-0.06, 0.04	-0.23,-0.02
		P-value	0.2609	0.0157

	DAS28-4 (ESR) <2.6 at month 6	Comparison with ADA	CP-5 mg BID	CP-10 mg BID	
		Difference versus ADA	1.16	6.32	
		95% CI for difference	-4.05, 6.38	0.28, 12.35	
		P-value	0.662	0.040	

Table 34 -Summary of efficacy for trial A3921046

Title: phase 3 randomized, double blind, one year, placebo-controlled study of efficacy and safety of 2 doses of CP-690,550 in patients with active RA on background DMARDs				
Study identifier	**A3921046**			
Design	Phase 3 randomized, one-year, double-blind, placebo controlled, parallel group study in 795 patients with active RA and inadequate response to at least one DMARD. Patients were randomized in a 4:4:1:1 ratio to one of four parallel treatment sequences: (1) CP-690,550 5 mg BID, (2) CP-690,550 10 mg BID, (3) placebo BID →CP-690,550 5 mg BID at month 3 or 6, (4) placebo BID → CP-690,550 10 mg BID at month 3 or 6. Advancement from placebo to CP-690,550 occurred at month 3 for the nonresponders; all remaining placebo-treated patients were advanced at Month 6			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 months 6 months	
Hypothesis	Superiority versus placebo			
Treatments groups	CP-690,550 5 mg BID (sequence 1)		N=315, one year	
	CP-690,550 10 mg BID (sequence 2)		N=318, one year	
	placebo →CP-690,550 5 mg (sequence 3)		N=79, 3 to 6 months	
	placebo →CP-690,550 10 mg (sequence 4)		N=80, 3 to 6 months	
Endpoints and definitions	**Primary endpoint**	ACR 20 at month 6		
	Primary endpoint	Change from baseline HAQ-DI at month 3		
	Primary endpoint	DAS28-4 (ESR) < 2.6 at month 3		
Database lock	<date>			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	**Full analysis set (FAS**) : all patients who were randomized to study and received at least 1 dose of study drug at month 3			
Descriptive statistics and estimate variability	Treatment group	**placebo**	**CP-690,550 5 mg BID**	**CP-690,550 10 mg BID**
	Number of subject	157	309	311
	ACR 20 at month 6	**31.21%**	**52.73%**	**58.25%**

	Number of subject	147	292	292
	Change from baseline HAQ-DI at month 3	-0.21	-0.46	-0.56
	Number of subject	136	241	248
	DAS28-4 (ESR) < 2.6 at month 3	5.15	13.69	16.53

Effect estimate per comparison	**ACR 20 at month 6**	Comparison with placebo	**CP-690,550 5 mg BID**	**CP-690,550 10 mg BID**
		Difference versus placebo	21.52	27.04
		95% CI for difference	12.39, 30.65	17.94, 36.13
		P-value	<0.0001	<0.0001
	Change from baseline HAQ-DI at month 3	Difference versus placebo	-0.26	-0.35
		95% CI for difference	-0.35, -0.16	-0.35, -0.44
		P-value	<0.0001	<0.0001
	DAS28-4 (ESR) < 2.6 at month 6	Difference versus placebo	8.54	11.38
		95% CI for difference	2.83, 14.25	5.45, 17.31
		P-value	0.0033	0.0001
Notes	N= number of patients			
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >**			

Table 35 - Summary of efficacy for trial A3921032

Title: phase 3, Randomized, Double-Blind, 6 months duration, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of CP-690,550 in Patients with Active Rheumatoid Arthritis on Background Methotrexate with Inadequate Response to TNF Inhibitors		
Study identifier	**A392132**	
Design	399 patients were randomized in a 2:2:1:1 ratio to one of the following four parallel treatment sequences: (1) CP-690,550 5 mg BID, (2) CP-690,550 10 mg BID, (3) placebo BID→ CP-690,550 5 mg BID at Month 3, (4) placebo BID → CP-690,550 10 mg BID at Month 3. Following 3 months of treatment, patients who first received placebo switched to CP-690,550 in a blinded manner at either 5 mg or 10 mg for the remainder of the 6-month study.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	3 months (PC period) 3 month
Hypothesis	Superiority versus placebo	
Treatments groups	CP-690,550 5 mg BID (sequence 1)	N=133, 6 months
	CP-690,550 10 mg BID (sequence 2)	N=134, 6 montsh
	placebo →CP-690,550 5 mg (sequence 3)	N=66, 3 months

	placebo →CP-690,550 10 mg (sequence 4)		N=66, 3 months
Endpoints and definitions	**Primary endpoint**	ACR 20 at month 3	
	Primary endpoint	Change from baseline HAQ-DI at month 3	
	Primary endpoint	DAS28-4 (ESR) < 2.6 at month 3	
Database lock	<date>		

Results and Analysis

Analysis description	**Primary analysis**			
Analysis population and time point description	**FAS (full analysis data set)**			
Descriptive statistics and estimate variability	**Treatment group**	**placebo**	**CP-690,550 5 mg BID**	**CP-690,550 10 mg BID**
	Number of subject	131	133	133
	ACR 20 at month 3	24.43	41.67	48.12
	Number of subject	118	117	125
	Change from baseline HAQ-DI at month 3	-0.18	-0.43	-0.46
	Number of subject	120	199	125
	DAS28-4 (ESR) < 2.6 at month 3	1.67%	6.72%	11.20%

Effect estimate per comparison	**ACR 20 at month 3**	Comparison with placebo	**CP-690,550 5 mg BID**	**CP-690,550 10 mg BID**
		Difference versus placebo	17.23	23.69
		95% CI for difference	6.06, 28.41	12.45, 34.92
		P-value	0.0024	<0.0001
	Change from baseline HAQ-DI at month 3	Comparison with placebo	**CP-690,550 5 mg BID**	**CP-690,550 10 mg BID**
		Difference versus placebo	-0.25	-0.28
		95% CI for difference	-0.36, -0.15	-0.38, -0.17
		P-value	<0.0001	<0.0001
	DAS28-4 (ESR) < 2.6 at month 3	Comparison with placebo	**CP-690,550 5 mg BID**	**CP-690,550 10 mg BID**
		Difference versus placebo	5.05	9.53
		95% CI for difference	0.00, 10,10	3.54, 15.51
		P-value	0.0496	0.0017
Notes				
Analysis description	**<Secondary analysis> <Co-primary Analysis> <Other, specify: >**			

Analysis performed across trials (pooled analyses and meta-analysis)

Post-hoc comparative analyses across all Phase III studies

Comparison of efficacy (signs, symptoms and physical function) results across studies:

Table 36 - ACR20 Response Rates (co-primary endpoint, FAS, NRI)

	n/N (%)	Difference from Placebo	95% CI Bounds		p-Value
			Lower	Upper	
Study A3921044 (Month 6)					
Tofacitinib 5 mg BID	141/269 (52.42)	26.38	17.10	35.67	<0.0001
Tofacitinib 10 mg BID	173/278 (62.23)	36.20	27.08	45.32	<0.0001
Placebo	38/146(26.03)				
Study A3921045 (Month 3)					
Tofacitinib 5 mg BID	131/210 (62.38)	33.38	22.33	44.43	<0.0001
Tofacitinib 10 mg BID	137/206 (66.50)	37.50	26.52	48.49	<0.0001
Placebo	29/100 (29.00)				
Study A3921046 (Month 6)					
Tofacitinib 5 mg BID	151/270 (55.93)	24.53	14.76	34.30	<0.0001
Tofacitinib 10 mg BID	169/272 (62.13)	30.74	21.06	40.42	<0.0001
Placebo	43/137 (31.39)				
Study A3921064 (Month 6)					
Tofacitinib 5 mg BID	99/190 (52.11)	24.22	13.05	35.38	<0.0001
Tofacitinib 10 mg BID	98/190 (51.58)	23.69	12.52	34.86	<0.0001
Adalimumab 40 mg SC QOW	90/193 (46.63)	18.74	7.62	29.87	0.0009
Placebo	29/104 (27.88)				

BID=twice daily, SC=subcutaneous, QOW=every other week, CI=confidence interval, n=number of subjects meeting criteria, N=number of subject analysed, NRI=non-responder imputation, FAS=full analysis set, ACR20=American College of Rheumatology ≥20% improvement, mg=milligram.

Table 37- ACR50 Response Rates (secondary endpoint, FAS, NRI)

	n/N (%)	Difference from Placebo	95% CI Bounds		p-Value
			Lower	Upper	
Study A3921044 (Month 6)					
Tofacitinib 5 mg BID	86/269 (31.97)	23.75	16.61	30.88	<0.0001
Tofacitinib 10 mg BID	125/278 (44.96)	36.74	29.39	44.09	<0.0001
Placebo	12/146 (8.22)				
Study A3921045 (Month 3)					
Tofacitinib 5 mg BID	70/210 (33.33)	21.33	12.32	30.35	<0.0001
Tofacitinib 10 mg BID	77/206 (37.38)	25.38	16.20	34.56	<0.0001
Placebo	12/100 (12.00)				
Study A3921046 (Month 6)					
Tofacitinib 5 mg BID	96/270 (35.56)	23.14	15.20	31.08	<0.0001
Tofacitinib 10 mg BID	106/272 (38.97)	26.56	18.55	34.56	<0.0001
Placebo	17/137 (12.41)				
Study A3921064 (Month 6)					
Tofacitinib 5 mg BID	71/190 (37.37)	24.86	15.50	34.23	<0.0001
Tofacitinib 10 mg BID	66/190 (34.74)	22.23	12.95	31.52	<0.0001
Adalimumab 40 mg SC QOW	52/193 (26.94)	14.44	5.52	23.36	0.0015
Placebo	13/104 (12.50)				

FAS=full analysis set, NRI=non-responder imputation, BID=twice daily, SC=subcutaneous, QOW=every other week, CI=confidence interval, n=number of subjects meeting criteria, N=number of subject analysed, ACR50=American College of Rheumatology ≥50% improvement, mg=milligram.

Table 38 - ACR70 Response Rates (secondary endpoint, FAS, NRI)

	n/N (%)	Difference from Placebo	95% CI Bounds		p-Value
			Lower	Upper	
Study A3921044 (Month 6)					
Tofacitinib 5 mg BID	38/269 (14.13)	12.75	8.18	17.32	<0.0001
Tofacitinib 10 mg BID	64/278 (23.02)	21.65	16.35	26.94	<0.0001
Placebo	2/146 (1.37)				
Study A3921045 (Month 3)					
Tofacitinib 5 mg BID	35/210 (16.67)	11.67	5.06	18.27	0.0005
Tofacitinib 10 mg BID	44/206 (21.36)	16.36	9.32	23.40	<0.0001
Placebo	5/100 (5.00)				
Study A3921046 (Month 6)					
Tofacitinib 5 mg BID	37/270 (13.70)	11.51	6.73	16.29	<0.0001
Tofacitinib 10 mg BID	45/272 (16.54)	14.35	9.30	19.40	<0.0001
Placebo	3/137 (2.19)				
Study A3921064 (Month 6)					
Tofacitinib 5 mg BID	38/190 (20.00)	18.07	11.80	24.34	<0.0001
Tofacitinib 10 mg BID	41/190 (21.58)	19.65	13.23	26.07	<0.0001
Adalimumab 40 mg SC QOW	18/193 (9.33)	7.40	2.52	12.28	0.0029
Placebo	2/104 (1.92)				

FAS=full analysis set, NRI=non-responder imputation, BID=twice daily, SC=subcutaneous, QOW=every other week, CI=confidence interval, n=number of subjects meeting criteria, N=number of subject analysed, ACR70=American College of Rheumatology ≥70% improvement, mg=milligram.

HAQ-DI (co-primary endpoint at month 3 for all the second line studies)

Table 39 - Summary of LS Mean Changes from Baseline in HAQ-DI at Month 3 in Studies A3921044, A3921045, A3921046, and A3921064 (FAS, Longitudinal Model)

	N	LS Mean Change from Baseline	LS Mean Difference from Placebo	95% CI Bounds		p-Value
				Lower	Upper	
Study A3921044						
Tofacitinib 5 mg BID	256	-0.41	-0.25	-0.35	-0.16	<0.0001
Tofacitinib 10 mg BID	271	-0.55	-0.39	-0.49	-0.30	<0.0001
Placebo	140	-0.16				
Study A3921045						
Tofacitinib 5 mg BID	207	-0.51	-0.36	-0.48	-0.24	<0.0001
Tofacitinib 10 mg BID	195	-0.56	-0.41	-0.53	-0.28	<0.0001
Placebo	91	-0.16				
Study A3921046						
Tofacitinib 5 mg BID	255	-0.49	-0.27	-0.37	-0.17	<0.0001
Tofacitinib 10 mg BID	261	-0.56	-0.34	-0.44	-0.24	<0.0001
Placebo	128	-0.22				
Study A3921064						
Tofacitinib 5 mg BID	182	-0.55	-0.31	-0.43	-0.18	<0.0001
Tofacitinib 10 mg BID	179	-0.62	-0.37	-0.50	-0.25	<0.0001
Adalimumab 40 mg SC QOW	184	-0.50	-0.26	-0.38	-0.14	<0.0001
Placebo	96	-0.24				

BID=twice daily, SC=subcutaneous, QOW=every other week, CI=confidence interval, N=number of subject analysed, LS=least squares, FAS=full analysis set, HAQ-DI=health assessment questionnaire disability index, mg=milligram.

2) Composite disease activity measures

Remission rate -DAS-28(ESR) <2.6

Table 40 - Proportion of Subjects Achieving Remission as Defined by Index-based Composite Disease Activity Measures at Months 3 and 6 in Studies A3921044, A3921045, A3921046, and A3921064 (2nd Line Population, FAS, NRI).

	DAS28-4(ESR)[1] <2.6		DAS28-4(CRP)[2] <2.6		SDAI ≤3.3[3]		CDAI ≤2.8[4]	
	Month 3	Month 6	Month 3	Month 6	Month 3	Month 6	Month 3	Month 6
Study A3921044 (6M)								
Tofacitinib 5 mg BID	5.58†	8.15*	20.4***	22.7***	6.32***	8.18***	6.69***	9.67***
Tofacitinib 10 mg BID	11.9***	15.7***	29.6***	36.5***	6.50***	15.5***	6.14***	15.2***
Placebo	1.61	1.61	5.48	4.79	0	0.68	0	1.37
Study A3921045[a]								
Tofacitinib 5 mg BID	5.97	NA	20.5***	NA	5.24†	NA	5.71†	NA
Tofacitinib 10 mg BID	10.3†	NA	24.8***	NA	10.2***	NA	9.76***	NA
Placebo	3.19	NA	5.00	NA	1.00	NA	1.00	NA
Study A3921046 (6M)								
Tofacitinib 5 mg BID	8.48***	8.85*	20.4***	21.5***	5.19***	6.30†	4.81**	6.30
Tofacitinib 10 mg BID	10.6***	13.8***	23.5***	32.4***	7.35***	11.0***	7.35***	11.0**
Placebo	0.79	2.34	5.11	6.57	0	2.19	0	2.92
Study A3921064 (6M)								
Tofacitinib 5 mg BID	5.81†	6.40†	18.4***	22.6***	4.21	5.79	4.74†	5.79
Tofacitinib 10 mg BID	7.06*	12.9***	17.9***	25.3***	7.37*	8.95*	6.32*	8.95*
Adalimumab 40 mg SC QOW	4.07	6.40†	14.5***	17.6*	3.63	6.22	2.07	5.18
Placebo	1.11	1.11	2.94	6.86	0.98	1.96	0.96	1.92

*** p ≤0.0001; ** p ≤0.001; * p ≤0.01; † p ≤0.05 versus placebo.
Primary time points were Month 3 for Study A3921045 and Month 6 for Studies A3921044, A3921046, and A3921064.
BID=twice daily, SC=subcutaneous, QOW=every other week, SDAI=simple disease activity index, CDAI= clinical disease activity index, DAS28=disease activity score 28 joints, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, mg=milligram, NRI=non-responder imputation, FAS=full analysis set, NA=not applicable.
a. Month 6 data is not applicable for Study A3921045.

DAS28-4(ESR) <2.6 reflects a treat to target of induction of "remission" although this endpoint is not sufficient on its own, given that a high contribution to the score is made by acute phase reactants (whether ESR or CRP are used) which can be influenced by a range of factors that are not necessarily directly related to the RA disease process itself.

The table above illustrates the higher responder rates with DAS28-4(CRP) compared to DAS28-4(ESR) which reflects the greater sensitivity of CRP to JAK inhibition, as has been reported previously. The DAS28 ESR endpoint was therefore chosen for the primary endpoints to avoid bias.

Evaluation of the inhibition of structural progression

The ability of tofacitinib to demonstrate radiographic evidence of the disease-modifying activity of inhibition of progression structural joint damage was assessed in 2 Phase III studies:

Study A3921044: A 2-year Phase III background MTX study including radiographic assessment of structural joint damage progression using mTSS in MTX-IR subjects with active RA.

Study A3921069: A 2-year Phase III monotherapy study of tofacitinib versus MTX including radiographic assessment of structural joint damage progression using mTSS in MTX-naïve subjects with active RA.

In addition to the 2 Phase III studies, several nonclinical and clinical studies were conducted to provide supportive evidence that tofacitinib inhibits the progression of structural joint damage and the results of these studies can be found in their respective study reports.

In the non-clinical collagen-induced and antigen-induced arthritis models, tofacitinib produced significant decreases in osteoclast numbers and histologically-assessed bone resorption in the paws of mice and rats.

Study A3921044 Background MTX. MTX-IR. 2 year study

In addition to the primary analysis described in the individual study section, a post-hoc subgroup analysis of patients with and without factors considered to be prognostic of a high degree of radiographic progression was performed. Prognostic factors including joint damage at baseline, elevated CRP, and the presence of autoantibodies including RF and antiCCP were used.

Increasing baseline CRP levels show a trend towards increased favouring of tofacitinib over placebo in demonstration of slowing of radiographic progression.

Additional prognostic factors for increased risk of structural damage progression are shown in Table 61 (below). The treatment effect was statistically significant for both tofacitinib 5 and 10 mg b.i.d. doses at Month 6 in subjects with a baseline mTSS above median, and for subjects who were both seropositive at baseline and had a baseline erosion score ≥ 3.

Table 41 – Summary of analyses in prognostic subsets for change from baseline in mTSS at month 6 in study A3921044

Analysis Set	Tofacitinib Dose	N	Difference from Placebo	95% CI		p-Value
				Lower	Upper	
Primary (FAS)	5 mg BID	277	-0.34	-0.73	0.04	0.0792
	10 mg BID	290	-0.40	-0.79	-0.02	0.0376
Baseline mTSS >Median	5 mg BID	137	-0.75	-1.42	-0.09	0.0267
	10 mg BID	145	-0.93	-1.60	-0.27	0.0059
Seropositive[a] and erosion score ≥ 3	5 mg BID	154	-0.72	-1.29	-0.15	0.0140
	10 mg BID	174	-0.83	-1.39	-0.27	0.0037
DAS28-4(ESR) >5.1	5 mg BID	250	-0.36	-0.79	0.07	0.0975
	10 mg BID	253	-0.47	-0.89	-0.04	0.0313

Source: A3921044 Year 1 CSR Table 14.2.15.1.6, a4.15, a4.17; Table 128q.14.2.15.1.6.
mTSS=modified total Sharp score, BID=twice daily, CI=confidence interval, DAS28=disease activity score 28 joints, ESR=erythrocyte sedimentation rate, mg=milligram, FAS=full analysis set, N=number of subjects analysed, CSR=clinical study report, LEP=linear extrapolation.
a. Rheumatoid factor antibody positive or cyclic citrullinated peptide antibody positive.

Study A3921044: Campaign 2

Campaign 2 involved a re-analysis of data at 6, 12 and 24 month time points.

Table 42 – Normal approximation of the proportion of subjects with no progression in mTSS at onths 6, 12, and 24 in study A3921044 Campaign 2

	n/N (%)	Difference From Placebo			
		Difference	95% CI for Difference		p-Value
			Lower	Upper	
Month 6					
Tofacitinib 5 mg BID	235/278 (84.53)	1.79	-5.78	9.38	0.6421
Tofacitinib 10 mg BID	251/291 (86.25)	3.52	-3.90	10.94	0.3527
Placebo	115/139 (82.73)				
Month 12					
Tofacitinib 5 mg BID	237/287 (82.58)	3.44	-4.61	11.49	0.4023
Tofacitinib 10 mg BID	248/298 (83.22)	4.08	-3.89	12.06	0.3155
Placebo	110/139 (79.14)				
Month 24					
Tofacitinib 5 mg BID	229/287 (79.79)	0.65	-7.54	8.85	0.8757
Tofacitinib 10 mg BID	244/298 (81.88)	2.74	-5.30	10.78	0.5041
Placebo	110/139 (79.14)				

Source: A3921044 Year 2 CSR Table 14.2.15.4.1.
BID=twice daily, CI=confidence interval, FAS=full analysis set, N=number of subjects analysed, n=number of subjects meeting criteria, LEP=linear extrapolation, CSR=clinical study report, mTSS=modified total Sharp score, mg=milligram.

Following the re-analysis of data for A3921044 in Campaign 2, the statistical significance for mean change from baseline mTSS (tofacitinib versus placebo) originally observed at 6 months for the 10 mg b.i.d. dose is no longer present and the 5 mg b.i.d. dose continues to be non-significant. The Applicant hypothesises that continuation of MTX in the placebo arm, even though the patients are MTX-IR (inadequate but not necessarily non-responsive), may have slowed structural progression compared to if the patients had been on no background therapy, thereby potentially reducing the treatment effect.

Further post-hoc evaluation to explore possible reasons for the difference in outcome between studies A3921044 and A3921069 has been conducted. This is discussed under conclusions on clinical efficacy and in the Benefit-Risk evaluation.

Systematic literature review and meta-analysis: mixed treatment comparison of the effect of tofacitinib versus biologic DMARDs

To assess the comparative efficacy of tofacitinib versus biologic treatments for RA patients who have had an inadequate response to a csDMARD, a systematic literature review and network meta-analysis (NMA) was conducted.

Table 43 – ACR20, ACR50, and ACR70 at 24 weeks: tofacitinib versus other monotherapies

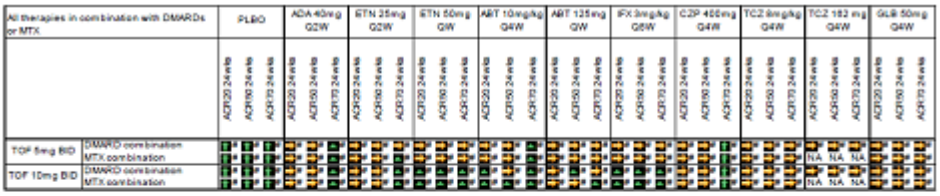
		PLBO			ADA 40mg Q2W			ADA 40mg QW			ETN 25mg Q2W			CZP 400mg Q4W			TCZ 8mg/kg Q4W		
		ACR20 24 wks	ACR50 24 wks	ACR70 24 wks	ACR20 24 wks	ACR50 24 wks	ACR70 24 wks	ACR20 24 wks	ACR50 24 wks	ACR70 24 wks	ACR20 24 wks	ACR50 24 wks	ACR70 24 wks	ACR20 24 wks	ACR50 24 wks	ACR70 24 wks	ACR20 24 wks	ACR50 24 wks	ACR70 24 wks
TOF 5mg BID	Monotherapies	↑#	↑#	↑#	→W	→W	→W	→W	→W	→W	↓#	↓#	↓#	→#	→#	→#	→#	→#	↓#
TOF 10mg BID	Monotherapies	↑#	↑#	↑#	→#	→#	→#	→#	→#	→#	→#	→#	→#	→#	→#	→#	→#	→#	→#

Source: Efficacy and Safety of Tofacitinib versus Biological Treatments for Rheumatoid Arthritis Patients Who have had an Inadequate Response with DMARDs.
BID=twice daily, mg=milligram, kg=kilogram, PLBO=placebo, ADA=adalimumab, ETN=etanercept, CZP=certolizumab pegol, TCZ=tocilizumab, TOF=tofacitinib, Q2(4)W=every 2(4) weeks, QW=every week, ACR20(50, 70)=American College of Rheumatology ≥20% (≥50%, ≥70%) improvement, wks=weeks, DMARD=disease-modifying anti-rheumatic drug.

More effective	↑#
Comparable, but likely to be favourable	↗#
Comparable	→#
Comparable, but likely to be unfavourable	↘#
Less effective	↓#

The network meta-analysis comparing tofacitinib as monotherapy with several biologic DMARDs supports that it is generally comparable as monotherapy with biologics in the second line treatment setting in RA.

Table 44 – ACR20, ACR50, and ACR70 at 24 weeks: tofacitinib versus other combination therapies (DMARD or MTX combination therapies)



Source: Efficacy and Safety of Tofacitinib versus Biological Treatments for Rheumatoid Arthritis Patients Who have had an Inadequate Response with DMARDs.
PLBO=placebo, ADA=adalimumab, mg=milligram, ETN=etanercept, CZP= certolizumab pegol, TCZ=tocilizumab, TOF=tofacitinib, IFX=infliximab, GLB=golimumab, ABT=abatacept, MTX=methotrexate, Q2(4,8)W=every 2(4,8) weeks, QW=every week, BID=twice daily, ACR20(50, 70)=American College of Rheumatology ≥20% (≥50%, ≥70%) improvement, wks=weeks, NA=not applicable, DMARD=disease-modifying anti-rheumatic drug.

These results support that tofacitinib at 5 mg b.i.d. and 10 mg b.i.d. in combination with MTX or other csDMARDs is comparably effective - in terms of inducing improvement in signs, symptoms and physical function - to biologic DMARDs in combination with MTX or other DMARDs in the 2nd line treatment setting. This supports the data from the pivotal Phase III studies in the 2nd line setting with tofacitinib in combination with MTX.

Pooled data from all submitted Phase II and Phase III studies

Pooled data from all Phase II and Phase III studies with duration ≥3 months were used to assess where there may be differences amongst subpopulations of subjects. Data were pooled to maximise the number of subjects in each of the subpopulations analysed, thereby allowing more robust assessments of differences between treatment groups.

Tofacitinib 5 mg BID appeared to be equally effective in reducing signs and symptoms of RA compared to placebo in all subgroups evaluated (as in ACR50, Figure 30). The probability ratios and, with few exceptions, the 95% CI of the probability ratios were all > 1, with overlapping CIs among the subsets of each characteristic assessed for ACR20, ACR50, and ACR70 response for the comparisons of the tofacitinib 5 mg BID dose group against placebo.

Across racial subgroups, there appeared to be a possible reduction in efficacy, possibly exposure-related, in African American patients. However, further efficacy analyses using continuous variables have demonstrated that tofacitinib at 5 mg b.i.d. appears as effective in African American patients as other races.

Clinical studies in special populations

Clinical studies that informed PK in special populations are included in the PK section.

Supportive studies

Long-term Extension studies to support persistence of efficacy

In addition to the 2-year results from Studies A3921044 and A3921069 presented above, durability of tofacitinib's efficacy is demonstrated in results of 2 LTE studies below:

In open-label LTE studies, tofacitinib 5 mg b.i.d. demonstrated sustained efficacy through 84 months of treatment as measured by ACR20 and DAS28-4(ESR) <2.6 response rates and improvement in physical function (change from baseline in HAQ-DI). Sustained efficacy was observed while on treatment. The risks of disease relapse are considered too great to recommend tapered withdrawal on induction of remission.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The results of six phase III trials were submitted in order to support this application.

Three studies, A3921044, A3921046 and A3921064 support the indication in a second line setting in combination with MTX. The overall population enrolled in these studies is represented by 2639 subjects treated in second line, a number considered adequate for a claim in this setting.

Studies A3921044, A3921046 and A3921064 evaluated the efficacy of tofacitinib, added to fixed and stable doses of background csDMARDs, mostly MTX, in treating the signs and symptoms and improving physical functioning in active RA. Study A3921044 included the evaluation of tofacitinib on bone structural damage.

One study, A3921045, supports the use of tofacitinib in a second line setting in monotherapy**,** in patients who are IR-MTX or where continued treatment with MTX is inappropriate. "Monotherapy" refers to the absence of concomitant therapy with any other DMARDs except anti-malarials.

Additional supportive evidence is derived from 2 studies, A3921032 and A3921069, performed in the third and first line population, respectively. The DMARD-naïve study (A3921069) was designed to further investigate the efficacy of tofacitinb on RA-induced bone damage compared to MTX.

Maintenance of treatment effect has been investigated in the OL A3921024 (ongoing) and A3921041 (completed, Japan study) long-term extension studies.

The enrolled patient population of the phase 3 trials is considered representative of the claimed indication, both in terms of duration of disease (a minimum of 2.6-3.3 years in the MTX naïve subjects to 11.2-13 years in TNFi-IR subjects; for DMARDs-IR subjects, the target population of the claimed indication, the mean duration of disease was 7-9 years), as well as clinical characteristics. Generally 60-80% of subjects were RF positive (higher percentage in the A3921069 study due to inclusion criteria aimed to select subjects prone to develop bone damage). In studies with bone endpoints (A3921044 and A3921069), the mean mTSS at baseline was double in the MTX-IR population (30.1-37.3) compared to MTX-naïve (16.5-20.3), correctly reflecting the expected different degree of bone damage at baseline in the two population settings.

Overall, subjects were correctly recruited according to prior RA treatments. However, the following inconsistencies are noted: i) in the A3921064 study, although only MTX-IR subjects were allowed, 9.2% of enrolled subjects were previously treated with an anti-TNFa or other bDMARD; ii) in the MTX naïve study (A3921069), 6.8% and 0.2% of subjects were previously treated with MTX and an anti-TNFa, respectively.

It is of note that the definition of non-responder or intolerant subject to cDMARDs or bDMARDs was up to the investigator, hence differences due to subjective evaluation or differences linked to clinical practice among countries might well have introduced a certain degree of heterogeneity in study results. Regarding duration of previous treatments, the majority of subjects had received a cDMARD for more than 12 months. However, in the monotherapy study in second line, (A3921045), for 50% and 24% of subjects no information is available regarding the duration of previous MTX or others csDMARDs, respectively.

Failure of TNFalpha drugs was due to lack of efficacy in 90% of subjects treated for more than 3 months, and in roughly 10% of those treated for less than 3 months; reasons due to Adverse events occurrence identified in 63% and 37% of subjects with > or < of 3 month bDMARD treatment, respectively.

Previous DMARD therapy varied across studies before study entry.For *A3921032, A3921044, and A3921064* studies background MTX was given in combination with Xeljanz and for the A3921046 patients were continued on whichever csDMARD (MTX or non-MTX) they had received prior to study entry. Of note, variable dosing of MTX was employed, depending on region, for example between Japan and Europe. This was considered acceptable in the CHMP scientific advice provided that appropriate numbers of EU patients dosed with at least 15 mg/week were included in the study. However, in the A3921045 study, in support of the monotherapy indication in second line**,** no information is available regarding the duration of previous MTX for roughly 50% of subjects. It is thus not possible to evaluate if these patients can be correctly considered as inadequately irresponsive to MTX.

The percentage of patients who completed the studies varied substantially, ranging from 66-69% in the A3921044 study to 95% in the A3921045 study. Discontinuations related to study drug were generally higher for adverse events as compared to lack of efficacy with the only exception of the A3021046 study (DMARDs-IR subjects) and the A3921069 study (MTX naïve subjects).

Primary and secondary endpoints generally reflect those used in RA clinical trials and are in line with the new revised CHMP guideline (CPMP/EWP/556/95 Rev. 2). In particular, the inclusion of remission (DAS28<2.6) is appreciated. Additional indexes of disease activity, CDAI and SDAI, have also been introduced, as secondary endpoint, to further explore tofacitinib efficacy in RA.

The use of ACR20 to define “non-responders” at month 3 was appropriate and adheres to ethical practice. This is a sensitive outcome measure which, if it is not met in an individual, can be used to determine a switch to active treatment.

A number of post hoc efficacy analyses were conducted to further understand and support the demonstration of the efficacy of tofacitinib in treating RA. All ACR composite response scores are limited by their reflection of relative and not absolute improvement. In contrast, the composite disease scores DAS28-4 (ESR/CRP) $\leq$ 3.2 to reflect low disease activity, or DAS28-4 (ESR/CRP) <2.6 to reflect remission, are not dependent on the level of baseline disease activity and may be more in line with a “treat to target approach”. On the other hand, these scores are limited by the high contribution made to them by change in acute phase reactant scores. The provision of a range of efficacy outcome measures is therefore encouraged.

In the case of tofacitinib, the use of DAS28-4(CRP) may raise particular concern in relation to a known early and potent inhibitory effect on CRP due to JAK inhibition, and therefore use of this endpoint may introduce

bias in favour of this class of drug. Nonetheless, there is good evidence that CRP is an effector molecule in the inflammatory response and is not an incidental bystander. To what extent CRP decline is prognostic of a sustained suppression of the inflammatory response is unclear however. The use of DAS28-4(ESR) as a primary endpoint and DAS28-4(CRP) as a secondary endpoint is therefore appropriate. It should be borne in mind also, however, that MTX produces an early suppression of both CRP and ESR and therefore the DAS28 scores may be particularly sensitive to the combination of MTX and tofacitinib due to the likelihood of an additive suppressive effect on acute phase reactants.

The modified total Sharp score (mTSS) is a validated radiographic method for assessing structural progression in rheumatoid arthritis and was included as a primary endpoint in two of the studies. A unit change in mTSS ≤ 0.5 is accepted as consistent with lack of structural progression.

Each of the studies included multiple primary endpoints which were prioritised according to the principal objectives of the study. The endpoints were analysed in a step-down hierarchy (see statistical analysis) that also took into account the different dose levels to avoid multiplicity issues. The order in which the endpoints were analysed reflected the clinical prioritisation according to the study objectives. Endpoints at subsequent points in the hierarchy were only considered to have formally reached significance if all the preceding endpoints had reached statistical significance. This is accepted as a valid method to avoid inflation of the type 1 error.

In several of the studies, ACR20 response rate was analysed as the first endpoint in the hierarchy but for the reasons discussed, this is not considered a sufficiently stringent endpoint for this to be considered indicative on its own of a positive efficacy outcome for a pivotal trial in the principal target population represented in the clinical programme. Statistical significance will therefore be required for ACR20 and at least the next subsequent endpoint in the hierarchy, for the trial to be considered as having reached a positive outcome, depending on the objective of the study. The use of ACR20 to identify non-responders among patients taking placebo so they can be converted to active treatment is nonetheless endorsed.

In addition to the efficacy analyses conducted to support the original submission, a number of post-hoc efficacy analyses were also conducted to provide further understanding and provide support for the demonstration of efficacy. In particular, composite disease activity scores – CDAI, SDAI and Boolean based scores - that may be less confounded by the response in acute phase reactants and therefore more reflective of genuine induction of low disease activity or remission were included. The provision of these additional analyses is welcomed.

Some concerns are raised over the handling of missing data. For ACR20, ACR50 and ACR70 the non-responder imputation approach is agreed.

For the total modified Sharp score the linear extrapolation approach ignores the potential for a loss of efficacy upon treatment discontinuation. Similarly for endpoints where it is assumed the data are missing at random (which is the assumption for the MMRM analysis being used) this will provide an estimate of the treatment effect which would have been seen if all patients had been able to continue with treatment for the entire planned study duration and ignores the likely loss of effect which would be seen with treatment discontinuation.

Efficacy data and additional analyses

Dose selection and schedule for Phase III:

Based on the DAS28-3(CRP) dose response analysis from the Phase II studies, the 5 mg and 10 mg b.i.d. doses were estimated to provide approximately 59% and 74% of the Emax , respectively, indicating that doses lower than 5 mg b.i.d. provide suboptimal efficacy while doses greater than 10 mg b.i.d. are unlikely to provide substantial improvements in mean DAS scores. Moreover, results from the ACR dose response analysis across the 4 Phase II studies, comparing the relative benefit of 5 mg b.i.d. versus 10 mg b.i.d. , expressed in terms of the ratio of estimated proportion of responders, were 1.04-1.11 for ACR20, 1.17- 1.47 for ACR50, and 1.27-1.77 for ACR70. Therefore, as expected, ACR20 is a sensitive but less discriminatory endpoint whereas ACR50 and ACR70 have more ability to discriminate levels of therapeutic activity with efficacious doses.

Overall, the Applicant has provided a robust data set to inform dose selection of 5 mg and 10 mg b.i.d. for the Phase III confirmatory studies. Although the 5 mg b.i.d. dose may appear sub-optimal, the Phase II primary analyses were conducted mostly at 12 weeks which is an early time point at which to convincingly demonstrate efficacy in rheumatoid arthritis.

Study A3921044 (background MTX, 2nd line treatment setting MTX-IR)

ACR20 response rate at month 6 was statistically significant for tofacitinib at both doses versus placebo ($p<0.0001$), with 51.46% of patients reaching the ACR20 threshold at the 5 mg b.i.d. dose.

The mean change from baseline in mTSS at month 6 reached statistical significance for the 10 mg b.i.d. dose only ($p=0.0376$) whereas the 5 mg b.i.d. dose failed to reach significance ($p=0.0792$) although it did show a trend to benefit over placebo. The radiographic scores need to be considered in the light of linear extrapolation of data in the placebo group, following treatment advancement. This is a recognised way to handle missing radiographic progression scores in RA trials. A number of measures were taken to minimise bias. The Applicant addressed concerns raised in relation to linear extrapolation for patients who withdrew from treatment, by using a multiple imputation procedure based on data from the placebo group. The results are consistent with the initially provided analyses. More mature data up to 24 months are presented in the final case study report and are discussed below.

In the 6 month analysis, the subsequent endpoints in the hierarchy (HAQ-DI) reached statistical significance for both tofacitinib doses ($p<0.0001$) compared with placebo as did DAS28-4(ESR) ($p=0.0034$ for tofacitinib 5 mg b.i.d. and $p<0.0001$ for 10 mg b.i.d.). These endpoints cannot be considered to have reached formal statistical significance, however, given that a preceding step (structural progression) in the hierarchy did not reach significance. That said, a 6 month time point is relatively early to observe an effect on radiographic progression and therefore the later radiographic data up to 24 months in the secondary analysis will also be considered (see below). The significant effects on HAQ-DI and DAS28-4(ESR) have some supportive value. 7.17% of patients receiving tofacitinib 5 mg b.i.d. achieved DAS28-4(ESR) < 2.6 at 6 months, compared with only 1.5% of patients in the placebo arm (despite treatment advancement to tofacitinib in some patients at 3 months and continuation of background MTX in all), indicating that the patient population is indeed clearly inadequately responsive to MTX. An added benefit of tofacitinib 5 mg b.i.d. to <6% of patients suggests the result has limited clinical relevance. This also contrasts with DAS28-4(ESR)<2.6 response rates at 6 months in study A3921069 (~15% with tofaticinib 5 mg b.i.d. with tofacitinib in this case as monotherapy) which is possibly explicable by a negative pharmacodynamic interaction between tofacitinib and MTX in study A3921044.

Secondary endpoints (1 year analysis) included ACR50 and ACR70 response rates which were consistent with the ACR20 response in showing benefit over placebo but with smaller numbers of responders as would be expected for more stringent endpoints.

Unlike the outcome at 6 months, at later assessment times in Campaign 2, the statistically significant difference even in the 10 mg b.i.d. group is not sustained and the 5 mg b.i.d. group continues to be non-significant. It is agreed that the continuation of MTX in the placebo arm, even though the patients are MTX-IR (inadequate but not necessarily non-responsive), may have slowed structural progression compared to if the patients had been on no background therapy, thereby potentially reducing the treatment effect.

ACR70 response rate was measured as a secondary endpoint. A minority of patients achieved the ACR70 response threshold (16.46%) in the tofacitinib 5 mg b.i.d. group which was less than in the placebo group (18.99%). The placebo data are confounded by treatment advancement at 3 and 6 months, but the data do not support a clinically relevant efficacy benefit of tofacitinib.

All treatment groups demonstrated an improvement in DAS28-4(ESR) scores that was sustained to 24 months. Although the data are confounded by advancement from placebo/MTX to tofacitinib/MTX at 3, or at most 6 months (depending on ACR20 response at 3 months), this is consistent with the other efficacy outcomes of this second analysis which do not indicate a clear efficacy benefit of tofacitinib in combination with MTX in this treatment line setting (MTX-IR). The effect of MTX on ESR also needs to be taken into consideration. Given that RA is a disease that can have a variable course and where a placebo effect on outcomes that include patient perception of benefit is a frequent finding, any apparent improvement has to be viewed with caution.

In addition to the primary analysis described in the individual study section, a post-hoc subgroup analysis of patients with and without factors considered to be prognostic of a high degree of radiographic progression was performed. Increasing baseline CRP levels show a trend towards increased favouring of tofacitinib over placebo in demonstration of slowing of radiographic progression. Given that CRP is not considered on its own to be a sufficient prognostic indicator of disease progression in RA, however, this would be unlikely to be useful clinically to define a more responsive subpopulation.

Further subpopulation analysis provided post-hoc during the procedure indicates that tofacitinib in combination with MTX does have a structure-preserving effect in at least those patients at increased risk of joint damage. This is discussed later in more detail.

Study A3921069 – Monotherapy, MTX naïve, head to head comparison with MTX, 2 years duration

ACR70 response rate is clearly superior for both tofacitinib doses compared to methotrexate alone. The difference is highly statistically significant ($p<0.0001$ for both tofacitinib 5 mg b.i.d. and 10 mg b.i.d.). 25.47% of patients achieved the ACR70 response threshold at 6 months at the tofacitinib 5 mg b.i.d. dose. ACR70 is a stringent endpoint which, although it reflects relative improvement, requires a 70% improvement from baseline in swollen/tender joint count and an improvement in other measures also. Given that patients, at least as judged by mean values for disease activity scores, were in a high activity band, this endpoint is clinically meaningful. Furthermore, there were 13.51% more patients who achieved the ACR70 threshold in the tofacitinib 5 mg b.i.d. group compared to the active comparator MTX group. In addition to tender and swollen joint counts, ACR70 also incorporates patient assessment of arthritis, HAQ-DI and acute phase reactants into the score and therefore provides a broad measure of signs and symptoms of RA.

The interpretation of the data is also strengthened by the lack of confounding by treatment advancement given that there was no requirement for a placebo arm as this was designed as a head to head superiority comparison.

Another principal objective of the study was to investigate radiographic progression to assess whether tofactinib administered as monotherapy would provide an efficacy gain compared to methotrexate in slowing or halting structural (joint) deterioration in this MTX-naïve population. Both tofacitinib treatment groups demonstrated statistically significant structural preservation compared with MTX as measured by the least squares (LS) mean change from baseline in mTSS at month 6 ($p=0.0006$ for 5 mg b.i.d. and $p<0.0001$ for 10 mg b.i.d.). Given that the preceding steps in the hierarchy had exceeded the specified statistical significance threshold of $p<0.05$ (ACR70 response rate compared with MTX for tofacitinib at 10 mg and 5 mg b.i.d.) the result of statistical significance is valid. An additional analysis has been provided to include 7 patients inappropriately excluded from the FAS and avoiding the linear extrapolation used for premature withdrawals which seems likely to overestimate the benefit received by patients who stop treatment early. The result of this analysis is consistent with the primary analysis. Secondary endpoints of change from baseline in erosion score and joint narrowing are statistically significant in favour of tofacitinib and consistent with mTSS.

Tofacitinib at both 5 mg and 10 mg b.i.d. doses was clearly superior over MTX in the prevention of further structural progression (non-progression) at 12 months ($p<0.0001$ for both tofacitinib 5 mg and 10 mg b.i.d. groups). Non-progression was defined as change from baseline in mTSS of ≤ 0.5 units which is recognised by clinical practitioners to reflect no clinically significant radiographic evidence of joint deterioration. At month 12, 81.16% of patients had demonstrated no radiographic progression from baseline in the tofacitinib 5 mg b.i.d. group compared to 64.71% in the methotrexate group which would support clinical relevance of the structural preservation.

The superior benefit of tofacitinib as monotherapy compared to MTX on structural preservation was maintained through to 24 months. This supports durable efficacy benefit while on treatment and raises the question whether remission will be maintained off treatment. This is discussed further, under the long term extension studies.

Study A3921069 had a clearly positive outcome in demonstrating compelling evidence of superior structural preservation and improvement in signs and symptoms of RA with tofacitinib at doses of 5 mg and 10 mg b.i.d. compared with methotrexate in this MTX naïve population with active rheumatoid arthritis. There were fewer discontinuations in the tofacitinib groups and a comparable incidence of adverse events (discussed in more detail under safety).

Study A3921045 Monotherapy tofacitinib in 2nd line treatment setting

The first two primary endpoints in the hierarchy (ACR20 response rate and change from baseline in HAQ-DI) reached statistical significance ($p<0.0001$) for both tofacitinib dose arms compared with placebo. The endpoints were measured at 3 months at which time no placebo treated patients had been advanced to active treatment and therefore the placebo group is pure.

Change from baseline in HAQ-DI was similarly significant ($p<0.0001$ for both tofacitinib doses compared to placebo) at 3 months. The Applicant re-analysed the data using using an analysis which more appropriately handles the likely loss of efficacy after treatment discontinuation.

In contrast, the third endpoint in the hierarchy (DAS28-4(ESR) <2.6 response rate), also measured at 3 months, failed to reach significance for either tofacitinib dose ($p=0.6179$ and $p= 0.1042$ for 5 mg b.i.d. and 10 mg b.i.d. respectively). The percentage of responders (5.60%) is similar however to other studies (see cross-study evaluation) and the lack of significance seems to be driven by a high placebo response (4.39%).

Nonetheless, it would be challenging to demonstrate induction of remission at 3 months (DAS28<2.6) and

therefore the failure of this endpoint to reach significance is not considered to demonstrate absence of efficacy. This is supported by the secondary endpoint DAS28-4(ESR)<3.2 (considered to represent a target of low disease activity) which did reach statistically significant difference from placebo at 3 months for both tofacitinib 5 mg b.i.d. ($p \leq 0.05$) and 10 mg b.i.d. ($p \leq 0.01$). Demonstration of low disease activity at 3 months is in line with a "treat to target" approach. The cross-study evaluation includes more stringent index-linked and Boolean based criteria.

In support of a relevant efficacy benefit at 3 months, ACR50 and ACR70 response rates both showed an early, statistically significant separation from placebo and by 3 months the difference was highly significant ($p<0.0001$ for ACR50 response with both tofacitinib doses; $p<0.001$ for ACR70 with tofacitinib 5 mg b.i.d.). the ACR50 response rate was ~ 30% and ACR70 ~15% for tofacitinib 5 mg b.i.d. at 3 months, compared with ~ 10% and 5% ACR50 and ACR70 response rates respectively for placebo at 3 months.

Although this study did not meet the 3rd primary endpoint in the pre-specified hierarchy it nonetheless suggests an overall picture of efficacy demonstration at 3 months given that all secondary endpoints are converging towards a conclusion of clinically relevant efficacy benefit (improvement in signs and symptoms) by 3 months of treatment. As discussed previously, ACR50 and in particular ACR70 can be considered acceptably stringent endpoints for this time point, regardless of the baseline level of disease severity, given that large percentage improvements in tender and swollen joint counts are required, along with similar improvements in at least 3 of the remaining 5 core ACR components. The DAS28-4(ESR) <3.2 can also be considered meaningful at this time point and was furthermore not contributed to by a suppressive effect of MTX as may have been the case in other studies.

The clear improvement over placebo at both tofacitinib doses in HAQ-DI by 3 months (a pre-specified primary endpoint) is a marker of meaningful improvement for the patient given that it reflects improvement in daily self-care, everyday tasks and mobility.

Structural progression was not assessed in this study but this is not considered a deficit given that the primary analysis was conducted at 3 months at which time point it would be unrealistic to expect to reveal any change in structural progression.

The overall conclusion from this study is that tofacitinib as monotherapy at a dose of 5 mg b.i.d. may be helpful in alleviating signs and symptoms in RA patients who have previously received at least one prior DMARD, to which they were inadequately responsive or intolerant.

Study A3921064 - Tofacitinib in combination with background MTX in 2nd line setting

Three of the primary endpoints for study A3921064 were the same as those for A3921044 (ACR20 response rate at 6 months, HAQ-DI at 3 months and DAS28(ESR)<2.6 at 6 months) and the studies were of a similar design (principally second line – patients in this study were required to be specifically MTX-IR – although 9.1% of patients had taken a prior biologic DMARD and 7.1% of patients had taken a prior TNFi. Given that a secondary objective of the study was to conduct a comparative evaluation with the TNF inhibitor adalimumab to which patients were randomised at the study outset, further information is requested in case of potential influence on the responsiveness of the adalimumab comparator group.

Unlike study A3921044, this study did not include the radiographic progression endpoint mTSS. As a consequence, all primary endpoints in the hierarchy did reach statistically significant superiority over placebo for both tofacitinib doses. The last endpoint in the hierarchy (DAS28-4(ESR)<2.6) can therefore be considered to have demonstrated superior ability of tofacitinib over placebo to induce a target of disease activity consistent with "remission" of signs and symptoms (with the provisos discussed previously in relation

to this outcome measure) after 6 months of treatment (levels of significance being tofacitinib 5 mg b.i.d. p=0.0151; tofacitinib 10 mg b.i.d. p<0.0001). This result is seen despite treatment advancement of some patients from placebo to tofacitinib at 3 months due to no improvement in ACR20. The advantage of the HAQ-DI parameter at 3 months is that this is not confounded by treatment advancement in the placebo group and is superior for tofacitinib over placebo at both doses (p<0.0001). This indicates early improvement in physical function. The clinical relevance of the effect on DAS28-4(ESR)<2.6 response rate is called into question however.

A similar percentage of patients achieved DAS28-4(ESR) < 2.6 at 6 months in tofacitinib 5 mg b.i.d. treated patients (6.21%) compared with adalimumab (6.74%) versus placebo (1.09%). The DAS28-4(ESR)<2.6 response rates at 6 months for tofacitinib at 5 mg b.i.d. versus placebo are very similar to those seen at 6 months in study A3921044 (7.17% for tofacitinib 5 mg versus 1.55% in placebo) which was conducted in a similar population of patients. These consistent effects were seen despite treatment advancement to tofacitinib in some patients at 3 months and continuation of background MTX in all, indicating that the patient population is indeed clearly inadequately responsive to MTX. The comparison with adalimumab was not a primary objective of the study but it does suggest comparable performance of two products that have a different mechanism of action in that one is a specific biologic inhibitor of a cytokine signalling molecule (TNF) and the other is a small molecule inhibitor of JAK which is a downstream transducing enzyme in the common effector pathway in the immuno-inflammatory response.

A similar point is made to that for study A3921044 which is that an added benefit of tofacitinib 5 mg b.i.d. to ~6% of patients suggests the result has limited clinical relevance. Nonetheless this reflects a comparable benefit to that seen with adalimumab.

The applicant has provided a series of post-hoc cross-study evaluations (see section below on cross-study evaluations) which includes a number of additional efficacy measures including the more stringent index-based and Boolean composite disease activity scores where thresholds of low disease activity and remission have been defined. These indicate that tofacitinib as monotherapy performs comparably to tofacitinib in combination with MTX, across a range of outcome measures. Further subpopulation analyses provided by the applicant support these results. Although the applicant's prediction of an additive effect on cytokine inhibition when tofacitinib is combined with MTX might anticipate a greater clinical benefit with the combination, the results do not demonstrate this. However, it can be said that there is no clear signal of inferior efficacy benefit with the combination.

Study A3921046 - 2nd line treatment setting, background csDMARD

The primary endpoints were the same as for study A3921064 (MTX-IR, background MTX), and the results very similar, with primary endpoints in the hierarchy being met and DAS28-4(ESR)<2.6 response rate slightly more significant at p=0.0038 for tofacitinib 5mg b.i.d. This still reflected only 9.13% of patients reaching "remission" according to this criterion, and only 6-7% higher than placebo. Clinical relevance is therefore questioned. The primary efficacy results therefore look very similar to those for A3921046, suggesting that patients who were inadequately responsive to other DMARDs, albeit in a minority, behave similarly.

Study A3921032 - Background MTX, TNFi-IR patients

This study is clearly relevant to the 3rd line treatment setting and also includes 35% of patients who were multiple TNFi failures (2 – 4 previous TNFi's) so it can be considered relevant to patients who are in a late stage of the disease and who have few treatment options. In the context of this patient population it was extremely ambitious to include DAS28-4(ESR)<2.6 response rate – considered to reflect induction of disease

"remission" - and even more so at an early 3 month time point. DAS28-4(ESR)<2.6 response rate does just reach statistical significance for tofacitinib 5 mg b.i.d. (p=0.0496) but it reflects only 6.72% of patients who achieve this (compared with 1.67% in the placebo group). The secondary endpoints and post-hoc analyses that evaluate more stringent index-linked and Boolean composite endpoints of disease activity may help to inform the clinical relevance of this. Safety evaluation in this end of line treatment population is also important in case multiple rounds of biologic therapies coupled with a late stage of disease may result in increased susceptibility to immunocompromise.

ACR50 and ACR70 response rates at 3 months support clinical relevance of the DAS28-4(ESR)<2.6 response. ~20 – 30% of patients achieve ACR50 at 3 months and ~10% ACR70 at tofacitinib 5 mg b.i.d. which at this early time point supports a meaningful efficacy response in this late stage population. The fact that 80% of patients in the tofacitinib 5 mg b.i.d. arm, completed 6 months treatment (higher than the placebo group) suggests the treatment was overall reasonably tolerated. From an efficacy standpoint the study can be considered positive.

Analysis performed across trials (pooled analyses and meta-analysis)

A cross-study comparison appears to indicate that the only study in which the DAS28-4 <2.6 endpoint does not reach statistical significance is study A3921045 which was the tofacitinib monotherapy study in the 2nd line treatment setting. However as discussed in the section on the individual study, the lack of statistical significance seems to be driven by a high placebo effect. Additional secondary efficacy endpoints are therefore taken into consideration.

Overall, these cross-study evaluations indicate consistency of benefit in signs, symptoms and physical function across the studies, whether tofacitinib was in combination with MTX or not. The stringent index-based composite disease activity scores (SDAI and CDAI) which were analysed post-hoc suggest that tofacitinib as monotherapy performs at least as well as tofacitinib in combination with background MTX in the 2nd line treatment setting with regard to remission of signs and symptoms and improvement in physical function.

There is a clear difference between the two main studies to investigate structural progression (A3921069 and A3921044), as was described in the sections on the individual studies.

The post-hoc data provided by the Applicant for study A3921044 suggest that there may be a responsive subset to the 5 mg b.i.d. dose within the overall population in which the subset is defined by high baseline mTSS and/or the combination of seropositivity and erosion score ≥ 3.

Further post-hoc subpopulation analyses provided by the Applicant suggest that patients with high radiographic scores at baseline, high CRP and more than 3 erosions exhibit the greatest structural benefit. And yet, in a limited post-hoc analysis of patients with pre-erosive disease (conducted in response to a question raised on potential for pre-emptive benefit) , there was also an indication of a structure-preserving effect. It may therefore be that the apparently greater structural benefit in poor prognostic patient subsets is because at the commencement of treatment, they are already on an established structural progression trajectory and are therefore more sensitive to revelation of benefit compared to placebo over a relatively short time window. Rather than there being an innate biological difference in structural preservation response between different prognostic subsets. This supports a lack of need to tailor treatment to different prognostic subsets.

2.5.4. Conclusions on the clinical efficacy

Tofacitinib at a dose of 5 mg b.i.d., whether as monotherapy or in combination with MTX, produces clinically relevant efficacy benefit on signs, symptoms and physical function in all treatment line settings.

The data appear to indicate that there may be difference in structural preservation outcome potentially due to treatment line setting or the administration of tofacitinib in combination with MTX compared with tofacitinib as monotherapy. Two possibilities were considered: whether the MTX inadequately responsive population was less sensitive to revelation of structural benefit due to the likelihood of a smaller potentially responsive subset and a lower rate of structural progression in this treatment setting; or, if the combination of MTX with tofacitinib was exerting a negative effect on structural preservation, possibly due to a negative pharmacodynamic interaction.

Overall, the data point more towards the difference in structural outcome between these studies as due to differences in sensitivity of the respective populations to reveal a clear treatment benefit over a relatively short time period.

The data also support that tofacitinib when administered in combination with MTX has comparable efficacy to tofacitinib administered as monotherapy in all patient subsets, regardless of prognostic factors, and on all treatment outcomes including signs, symptoms, physical function and structural preservation.

With regard to the bDMARD inadequately responsive patient population, in a dedicated study that investigated such patients, there was a statistically significant difference between patients treated with tofacitinib 5 mg b.i.d compared to placebo in responder rates for attainment of DAS28-4(ESR) < 3.2 ("low disease activity") which is considered a sufficient efficacy target in this patient population. bDMARD-IR exhibit a higher incidence of herpes zoster (see also safety discussion and benefit-risk) compared with MTX-IR patients. The efficacy data in bDMARD-IR patients are limited by the lack of data on structural progression and attainment of a less stringent target outcome measure (low disease activity rather than remission). The indication agreed by CHMP gives the clinician scope to consider tofacitinib for an individual patient who has received prior bDMARD therapy, given that a sufficient efficacy benefit for this treatment line setting has been demonstrated and warnings in the product information and risk management plan are considered to be sufficient for judgement by the clinician of a patient's individual benefit-risk profile according to whether they may have received a prior biological therapy.

2.6. Clinical safety

The Grounds for Refusal related to the safety profile were:

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

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

magnitude of the severe risks and their management in clinical practice, which are not offset by the benefits of treatment.'

The main new data and analyses included in the present application to complete the safety characterisation of tofacitinib and address the CHMP Grounds for Refusal from the initial MAA and re-examination procedures are:

Immune Effect Assessment:
-6-month interim clinical data from an ongoing 2-year lymphocyte subset study;
-A clinical zoster vaccine study, to further understand the effect of tofacitinib on immune response in RA patients on background MTX.

Additional Safety Characterisation:

-Completed, ongoing and planned RA clinical studies: Updated safety information based on a 31 March 2015 data-cut.

-Risk Characterisation: to facilitate a comparison of incidence rates for key safety risks amongst tofacitinib-exposed and relevant second line comparator exposed EU populations by:

A literature review of observational studies
Meta-analyses for SI events and all malignancies (excluding NMSC)
Four retrospective cohort studies within 4 established European external RA registers to estimate background incidence rates of selected AEs.

Pharmacovigilance (PV) activities

-Post-marketing data; spontaneous safety information from over 3 years after the initial product approval in the United States (US), by providing PSURs.

-Post-authorisation observational safety studies; emerging safety data from 2 ongoing observational, post-authorisation safety studies from the US (CORRONA registry) and Japa

The safety data are presented in 3 pooled populations as follow:

1. Randomised Controlled Trials (RCTs): pooled Phase 2 and Phase 3 randomised controlled clinical trials.
2. LTE: pooled LTE studies A3921024 and A3921041.
3. All RA: integrated data from all RA controlled and LTE studies.

Adalimumab and MTX were each included as active comparators within a controlled clinical trial (Study A3921064 and Study A3921069, respectely) and are provided separately to retain the randomised and controlled nature of the comparison.

Patient exposure

The table below presents the number of subjects who received at least 1 dose of study drug, and the total and mean exposures to tofacitinib across the 3 safety populations for analysis of safety.

Table 45 - Tofacitinib Exposures in the 3 Safety Populations

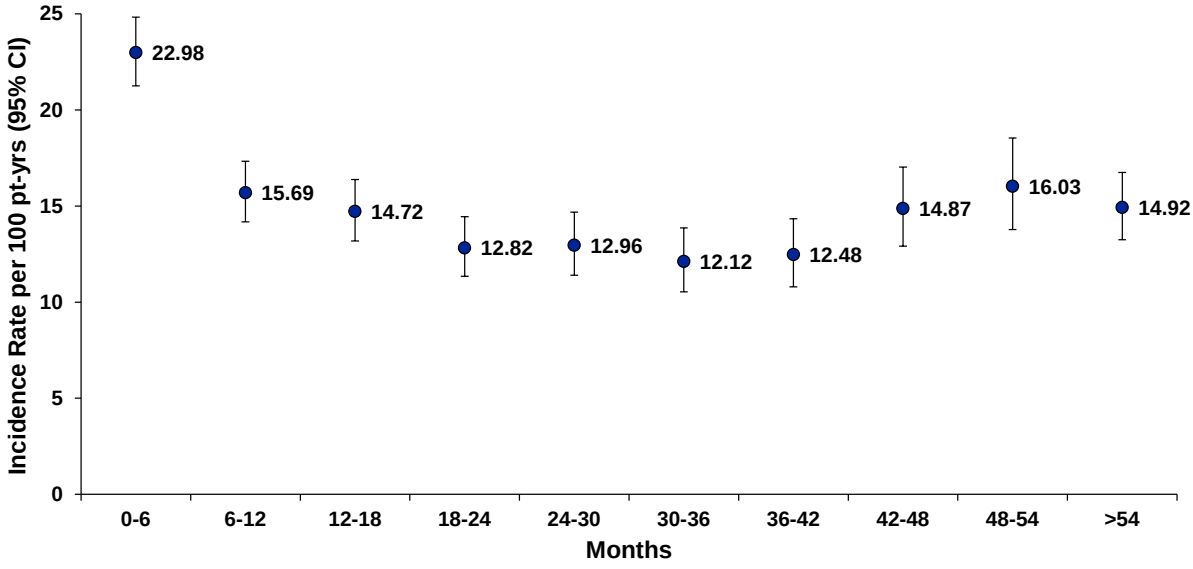
Population	Tofacitinib 5 mg BID			Tofacitinib 10 mg BID			All Tofacitinib Doses		
	Subjects (n)	Total Exposure (PY)	Mean Duration (Year)	Subjects (n)	Total Exposure (PY)	Mean Duration (Year)	Subjects (n)	Total Exposure (PY)	Mean Duration (Year)
RCTs	1849	1818.9	0.98	2024	1952.1	0.96	5368	4440.0	0.83
LTE									
Average Dose	1471	5278.0	3.55	3396	9647.8	2.81	4867	14925.8	3.03
All RA									
Average Dose	2239	6870.2	3.07	3955	12535.7	3.17	6194	19405.8	3.13
Constant Dose	2342	3623.4	1.55	2814	6701.8	2.38	NC	NC	NC

Source: P2P3 Table 2.1.3.2, LTE Tables 2.1.1, s18.2, P123LTE Tables 1.2.1.1.A, 1.5.1.1.A, 1031.1.2, 1031.1.3
BID=twice daily, LTE=long-term extension, NC=not calculated, PY=patient-year, RA=rheumatoid arthritis, RCT=randomised controlled trial

During the first 12 months discontinuation occurred more frequently in tofacitinib 5 mg BID group (26.5%) compared to tofacitinib 10 mg group (21.4%) and adalimumab group (20.6%). The most common reason of discontinuation related to study drug was adverse event, with a higher incidence in tofacitinib 5 mg BID group.

In all RA population (March 31 2015) approximately half of the subjects remained on study drug (48.1% discontinued). Adverse events (23.3%) were the most common reason for discontinuation related to study drug.

Figure 20 - Exposure Estimates and Incidence Rates for Discontinuations by 6-month Intervals (All RA)



	0-6	6-12	12-18	18-24	24-30	30-36	36-42	42-48	48-54	>54
N	6194	5309	4851	4454	4146	3684	3415	3035	2644	2004
n	646	392	335	272	247	211	198	208	181	289
PY for event	2810.63	2497.72	2276.15	2120.95	1905.69	1741.65	1587.10	1399.17	1129.46	1936.84

Adverse events

The analysis of adverse events is largely focused on the RCTs (up to 2 years of exposure) and all RA populations.

RCT Population

Tofacitinib vs Placebo (0-3 Month)

Table 46 - Number (%) of Subjects with Treatment-emergent Adverse Events with Tofacitinib vs Placebo (RCTs, 0-3 Month)

Number (%) Of Subjects	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo
Subjects Evaluable For Adverse Events	1849	2024	4681	1079
Subjects With Adverse Events	951 (51.4)	1110 (54.8)	2500 (53.4)	559 (51.8)
Subjects With Serious Adverse Events	49 (2.7)	46 (2.3)	117 (2.5)	29 (2.7)
Subjects With Severe Adverse Events	67 (3.6)	60 (3.0)	151 (3.2)	34 (3.2)
Subjects Discontinued Due To Adverse Events	71 (3.8)	79 (3.9)	191 (4.1)	37 (3.4)

The sum of tofacitinib 5 mg BID and 10 mg BID doses may not equate to the all doses column. This is because there were subjects in the RCTs who received doses different than 5 mg BID and 10 mg BID or received placebo initially; these subjects are not counted in 5 mg BID or 10 mg BID but are counted in all doses.
MedDRA (v18.0) coding dictionary applied.
BID=twice daily, MedDRA=Medical Dictionary for Regulatory Activities, RCT=randomised controlled trial.

Incidence Rate (0-24 Month)

Table 47 - Exposure Estimates and Incidence Rates for Treatment-emergent Adverse Events (RCTs, 0-24 Month)

Treatment Group	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo
Treatment Duration	Up to 24 Months	Up to 24 Months	Up to 24 Months	Up to 6 Months
Subjects with Exposure	1849	2024	5368	1079
Subjects with Event (n)	1356	1495	3693	580
Total PY Exposure for Event	746.6	758.8	1906.0	184.2
Incidence Rate/100 PY	181.62	197.02	193.76	314.96
(95% CI)	(172.08, 191.55)	(187.16, 207.26)	(187.56, 200.11)	(289.85, 341.67)

The sum of tofacitinib 5 mg BID and 10 mg BID doses may not equate to the all doses column. This is because there were subjects in the RCTs who received doses different than 5 mg BID and 10 mg BID or received placebo initially; these subjects are not counted in 5 mg BID or 10 mg BID but are counted in all doses. BID=twice daily, CI=confidence interval, PY=patient-year, RCT=randomised controlled trial.

In Study 1064 a similar percentage of subjects receiving tofacitinib 5 mg BID experienced TEAEs as compared to those treated with adalimumab (73% each). However, there was an increase in serious or severe TEAEs in patients receiving tofacitinib compared with adalimumab-treated patients.

When compared with MTX (Study 1069), the occurrence of TEAEs in subjects receiving tofacitinib 5 mg BID was 79.6% and MTX was 79%. No differences were noted in serious or severe TEAEs for tofacitinib compared with MTX treated.

All RA Population

Over time, the incidence rate [per 100 PY (95% CI)] of adverse events for all doses of tofacitinib in all RA population [136.87 (133.29, 140.52)] was lower compared to the rate obtained from the RCT population [193.76 (187.56, 200.11).

Tofacitinib Monotherapy vs Background DMARD Studies

Table 48 - Exposure Estimates and Incidence Rates for Treatment-emergent Adverse Events: Monotherapy vs Background DMARD Studies (RCTs, 0-24 Month)

Treatment Group	Tofa Monotherapy Studies		Tofa with Background DMARDs	
	5 mg BID	10 mg BID	5 mg BID	10 mg BID
Subjects with Exposure	778	842	1071	1182
Subjects with Events (n)	545	626	811	869
Total PY Exposure for Event	324.2	315.2	422.4	443.6
Incidence Rate/100 PY (95% CI)	168.11 (154.29, 182.84)	198.61 (183.35, 214.79)	191.98 (178.99, 205.66)	195.89 (183.08, 209.36)

BID=twice daily, CI=confidence interval, DMARD=disease-modifying antirheumatic drug, PY=patient-year, RCT=randomised controlled trial, Tofa=tofacitinib

Common Adverse Events

Table 49 - Treatment-emergent Adverse Events with ≥2% Occurrence, by Preferred Term, in Any Treatment Group (RCTs, 0-3 Month)

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo
Subjects Evaluable For Adverse Events	1849	2024	4681	1079
Number (%) of Subjects with Adverse Events	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders	168 (9.1)	191 (9.4)	422 (9.0)	86 (8.0)
Gastritis	17 (0.9)	28 (1.4)	52 (1.1)	9 (0.8)
Constipation	27 (1.5)	29 (1.4)	64 (1.4)	13 (1.2)
Diarrhoea	64 (3.5)	56 (2.8)	141 (3.0)	28 (2.6)
Dyspepsia	25 (1.4)	39 (1.9)	71 (1.5)	14 (1.3)
Nausea	52 (2.8)	57 (2.8)	137 (2.9)	25 (2.3)
General disorders and administration site conditions	12 (0.6)	16 (0.8)	35 (0.7)	1 (0.1)
Fatigue	12 (0.6)	16 (0.8)	35 (0.7)	1 (0.1)
Infections and infestations	189 (10.2)	193 (9.5)	473 (10.1)	106 (9.8)
Bronchitis	25 (1.4)	23 (1.1)	64 (1.4)	14 (1.3)
Nasopharyngitis	64 (3.5)	63 (3.1)	160 (3.4)	34 (3.2)
Upper respiratory tract infection	71 (3.8)	72 (3.6)	161 (3.4)	41 (3.8)
Urinary tract infection	39 (2.1)	40 (2.0)	105 (2.2)	21 (1.9)
Investigations	39 (2.1)	69 (3.4)	123 (2.6)	21 (1.9)
Blood creatine phosphokinase increased	13 (0.7)	42 (2.1)	56 (1.2)	4 (0.4)
Alanine aminotransferase increased	27 (1.5)	30 (1.5)	72 (1.5)	17 (1.6)
Musculoskeletal and connective tissue disorders	40 (2.2)	30 (1.5)	85 (1.8)	52 (4.8)
Arthralgia	19 (1.0)	20 (1.0)	47 (1.0)	25 (2.3)
Rheumatoid arthritis	21 (1.1)	11 (0.5)	40 (0.9)	28 (2.6)
Nervous system disorders	84 (4.5)	80 (4.0)	216 (4.6)	26 (2.4)
Headache	84 (4.5)	80 (4.0)	216 (4.6)	26 (2.4)
Skin and subcutaneous tissue disorders	9 (0.5)	20 (1.0)	45 (1.0)	8 (0.7)
Rash	9 (0.5)	20 (1.0)	45 (1.0)	8 (0.7)

Table 49 - Treatment-emergent Adverse Events with ≥2% Occurrence, by Preferred Term, in Any Treatment Group (RCTs, 0-3 Month)

System Organ Class Preferred Term	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo
Subjects Evaluable For Adverse Events	1849	2024	4681	1079
Number (%) of Subjects with Adverse Events	n (%)	n (%)	n (%)	n (%)
Vascular disorders	34 (1.8)	55 (2.7)	103 (2.2)	9 (0.8)
Hypertension	34 (1.8)	55 (2.7)	103 (2.2)	9 (0.8)

The sum of tofacitinib 5 mg BID and 10 mg BID doses may not equate to the all doses column. This is because there were subjects in the RCTs who received doses different than 5 mg BID and 10 mg BID or received placebo initially; these subjects are not counted in 5 mg BID or 10 mg BID but are counted in all doses.
MedDRA (v18.0) coding dictionary applied.
BID=twice daily, MedDRA=Medical Dictionary for Regulatory Activities, n=number of subjects with event, RCT=randomised controlled trial.

LTE Population

The most common adverse events associated with long-term tofacitinib treatment were Infections and infestations, Gastrointestinal disorders, by SOC; and nasopharyngitis, upper respiratory tract infection, urinary tract infection by PT.

Serious adverse event/deaths/other significant events

Deaths

There were 26 subjects (including 3 subjects receiving adalimumab) deaths in the RCTs; 71 subject deaths and 1 foetal death in the LTE studies (39 deaths were reported in subjects receiving tofacitinib 5 mg BID and 32 deaths in subjects receiving tofacitinib 10 mg BID). Infections, malignancies and CV events were the most frequently reported reasons for death.

In All RA population a total of 51 deaths occurred among subjects receiving any dose of tofacitinib up to 30 days of last study treatment and the overall incidence rate [per 100 PY (95% CI)] for deaths was 0.26 (0.20, 0.35) with all doses of tofacitinib combined.

Serious Adverse Events

RCTs (0-3 Months): 3.1% (57/1849), 2.5% (51/2024), and 2.9% (31/1079) of the subjects in the tofacitinib 5 mg BID, 10 mg BID and placebo groups, respectively, experienced at least 1 serious adverse event. The most common SAEs for tofacitinib treatment were in the Infections and infestations SOC, the incidence of which was higher with tofacitinib (0.8% with either dose) than with placebo treatment (0.4%). By PT, the most frequently reported SAEs with tofacitinib were pneumonia (6 subjects, 0.1% with either dose) and herpes zoster (4 subjects, 0.1% with either dose); there were no cases of pneumonia or herpes zoster among subjects receiving placebo.

RCTs, (0-24 Month)

Table 50 - Exposure Estimates and Incidence Rates for Serious Adverse Events (RCTs, 0-24 Month)

Treatment Group	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Tofacitinib All Doses	Placebo
Treatment Duration	Up to 24 Months	Up to 24 Months	Up to 24 Months	Up to 6 Months
Number Subjects with Exposure	1849	2024	5368	1079
Number Subjects with Event	183	166	418	37
Total PY Exposure for Event	1748.4	1899.0	4307.6	282.8
Incidence Rate/100 PY (95% CI)	10.47 (9.01, 12.10)	8.74 (7.46, 10.18)	9.70 (8.80, 10.68)	13.08 (9.21, 18.04)

The sum of tofacitinib 5 mg BID and 10 mg BID doses may not equate to the all doses column. This is because there were subjects in the RCTs who received doses different than 5 mg BID and 10 mg BID or received placebo initially; these subjects are not counted in 5 mg BID or 10 mg BID but are counted in all doses.
BID=twice daily, CI=confidence interval, PY=patient-year, RCT=randomised controlled trial.

Study 1064 (0-12 Month): 15.7% (32/204) of the subjects receiving tofacitinib 5 mg BID, 12.4% (25/201) receiving 10 mg BID, and 9.3% (19/204) receiving adalimumab experienced at least 1 serious adverse event.

Study 1069, (0-24 Month): The overall percentages of subjects with SAEs were similar across the tofacitinib 5 mg BID, 10 mg BID and MTX arms (10.5%, 10.6% and 11.8% respectively).

LTE Population

Table 51 - Exposure Estimates and Incidence Rates for Serious Adverse Events (LTE)

Treatment Group	Tofacitinib All Doses	Average 5 mg BID	Average 10 mg BID
Subjects with Exposure	4867	1471	3396
Subjects with Events(n)	1303	431	872
Total PY Exposure for Event	13439.3	4698.4	8740.9
Incidence Rate/100 PY (95% CI)	9.67 (9.18, 10.24)	9.13 (8.33, 10.08)	9.95 (9.33, 10.66)

Source: LTE Table 6.5.1.
BID=twice daily, CI=confidence interval, LTE=long-term extension, PY=patient-year

Tofacitinib Monotherapy vs Background DMARD Studies

The incidence rate [per 100 PY (95% CI)] of serious adverse events: 5 mg BID: 3.44 (2.41, 4.76); 10 mg BID: 3.42 (2.42, 4.70)], monotherapy studies: 5 mg BID: 1.70 (0.91, 2.92); 10 mg BID: 1.79 (1.00, 2.95).

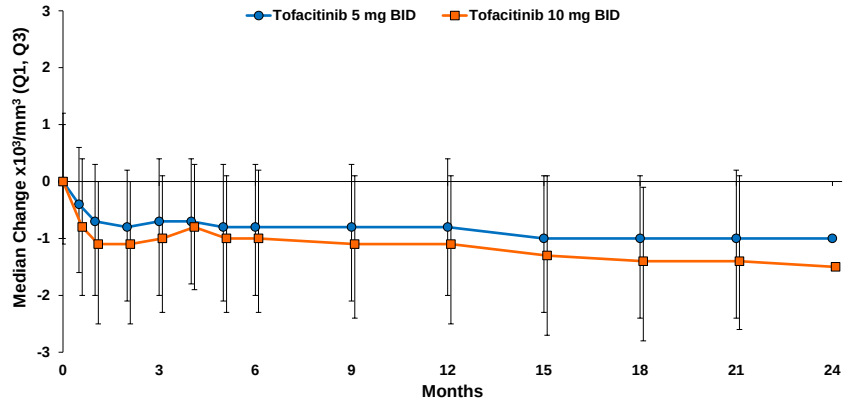
AEs of Special Interest (AESIs)

1. Serious infections
2. Herpes zoster
3. Opportunistic infections (OIs) excluding tuberculosis (TB)
4. TB
5. Malignancies
6. Major adverse cardiovascular events (MACE)
7. Gastrointestinal (GI) perforations
8. Hepatic safety
9. Interstitial lung disease (ILD)

1) Serious infections

Neutrophils

Figure 21 - Median Change from Baseline in Absolute Neutrophil Count (RCTs, 0-24 Month)



Number of Subjects													
5 mg	697	1745	1115	1695	713	317	1475	1008	949	525	508	487	458
10 mg	650	1887	1148	1848	725	318	1581	1107	1032	559	533	514	490

The table below shows the clinical correlates of changes in ANC in tofacitinib 5 mg arm .

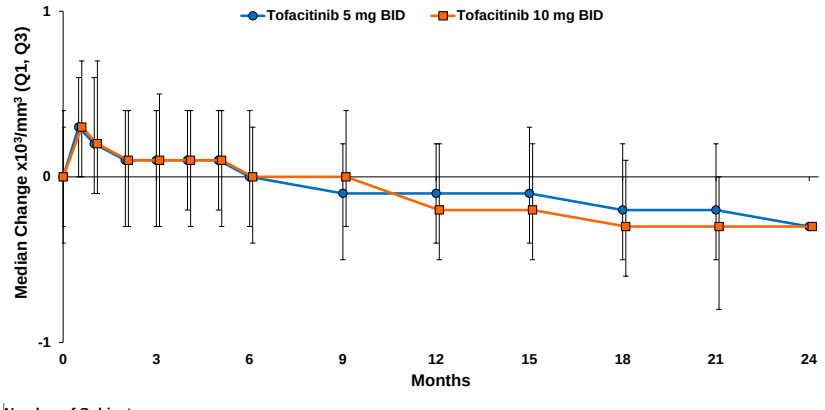
Table 52 - Number (%) of Subjects with Confirmed Neutropaenia by Presence of Infection (RCTs, 0-3 Month)

Confirmed ANC ($\times 10^3$ cells/mm^3)	Tofacitinib 5 mg BID Subjects Evaluable (N)	Subjects with Infections [n (%)]	Tofacitinib 10 mg BID Subjects Evaluable (N)	Subjects with Infections [n (%)]
≥2	1815	244 (13.4)	1973	274 (13.9)
<2 to ≥1.5	31	4 (12.9)	40	6 (15.0)
<1.5 to ≥0.5	3	0	11	2 (18.2)
<0.5	0	0	0	0

ANC=absolute neutrophil count, BID=twice daily, RCT=randomised controlled trial.

Lymphocytes

Figure 22 - Median Change from Baseline in Absolute Lymphocyte Count (ALC) (RCTs, 0-24 Month)



Number of Subjects													
5 mg	697	1745	1115	1695	712	316	1475	1007	949	525	508	487	458
10 mg	650	1887	1148	1848	725	318	1580	1107	1032	559	532	514	490

LTE studies: The median decrease in ALC from pretreatment baseline was approximately 25%.

In the All RA dataset, 69 (1.1%) subjects experienced a confirmed ALC <500 cells/mm^3. The majority were lymphopaenic at baseline (32%<1500 cells/mm^3, 51%<1000 cells/mm^3).

About 75% of these patients achieved ALC>500/mm^3 by a median of 3 weeks and 15 patients remained with ALC<500/mm^3 (8 out of which had ALC<1000 cells/mm^3 at baseline).

Confirmed ALC (Cells/mm^3)	Serious Infection			Opportunistic Infection			Herpes Zoster[a]			Malignancy[c]		
	N[b]	n	IR (95% CI)	N[b]	n	IR (95% CI)	N[b]	n	IR (95% CI)	N[b]	n	IR (95% CI)
≥2000	5558	80	2.26 (1.79, 2.81)	5581	4	0.112 (0.031, 0.288)	5558	103	2.98 (2.43, 3.62)	5558	14	0.393 (0.215, 0.660)
≥1500 to <2000	3954	119	2.49 (2.06, 2.98)	3961	10	0.208 (0.100, 0.383)	3907	167	3.67 (3.13, 4.27)	3961	17	0.353 (0.206, 0.566)
≥1000 to <1500	3768	201	2.70 (2.34, 3.10)	3784	25	0.333 (0.216, 0.492)	3663	275	4.01 (3.55, 4.51)	3786	30	0.400 (0.270, 0.570)
≥500 to <1000	1570	115	3.39 (2.80, 4.07)	1582	21	0.613 (0.380, 0.938)	1467	151	5.01 (4.24, 5.87)	1584	16	0.466 (0.266, 0.756)
<500	64	6	8.307 (3.05, 18.1)	64	1	1.391 (0.035, 7.750)	57	3	4.81 (0.992, 14.1)	65	1	1.381 (0.035, 7.694)

Immunology sub-study

Changes in LSC in Short-term Studies

Phase 2 studies showed:

-CD3$^+$, CD4$^+$, or CD8$^+$ T cells: median decreases of <8% from baseline

-NK cells: median reduction of 36%

-B cells: median increase of approximately 30%

Reversibility after Short-Term Treatment

Reversibility was assessed after 6 weeks of withdrawal from 6 weeks of tofacitinib treatment in Study A3921019.

T cells: distributions similar to those of placebo

The median % change for pre-treatment baseline at week 12 for NK and B cells was nearly 0.

Changes in LSC in Long-term Studies

Tofacitinib treatment resulted in median reductions of:

- 20% in CD3+ T cells
- 28% in CD4+ T cells
- 27% in CD8+ T cells

Conversely NK cells increased 73% and B cells 3%.

Table 53 - Number (%) of Infection Events by Nadir LSC Categorized by Values outside and within RA Reference Ranges (Phase 2 Studies)

	AI			SI			HZ		
	n	N	%	n	N	%	n	N	%
CD3+ T cell (>531 cells/mm^3)	272	1036	26.3	4	1035	0.39	7	1036	0.68
CD3+ T cell (≤531 cells/mm^3)	17	47	36.17	0	47	0.00	1	47	2.13
CD4+ T cell (>200 cells/mm^3)	89	344	25.87	3	344	0.87	1	344	0.29
CD4+ T cell (≤200 cells/mm^3)	3	4	75.00	0	4	0.00	0	4	0.00
CD4+ T cell (>400 cells/mm^3)	81	315	25.71	3	315	0.95	1	315	0.32
CD4+ T cell (≤400 cells/mm^3)	11	33	33.33	0	33	0.00	0	33	0.00
CD8+ T cell (>116 cells/mm^3)	83	325	25.54	3	325	0.92	0	325	0.00
CD8+ T cell (≤116 cells/mm^3)	9	23	39.13	0	23	0.00	1	23	4.35
NK cell (>35 cells/mm^3)	165	569	29.00	2	568	0.35	2	569	0.35
NK cell (≤35 cells/mm^3)	49	148	33.11	1	148	0.68	1	148	0.68
B cell (<365 cells/mm^3)	43	165	26.06	1	165	0.61	1	165	0.61
B cell (≥365 cells/mm^3)	246	917	26.83	3	916	0.33	7	917	0.76

Abbreviations: AI=All infections; B cell=B lymphocytes; CD=Cluster of differentiation; HZ=Herpes zoster; LSC=Lymphocyte subset count; n=Number of subjects with event; N=Total number of subjects in the category; NK cells=Natural killer cells; RA=Rheumatoid arthritis; SI=Serious infections; T cells=Thymus-derived (T) cells.
Cut off values represent lower reference values in RA patients (upper for B cells); CD4 threshold of 200 cells/mm^3 represents an additional cut-off commonly used in other disease areas.
Source: Table 930.7.30.

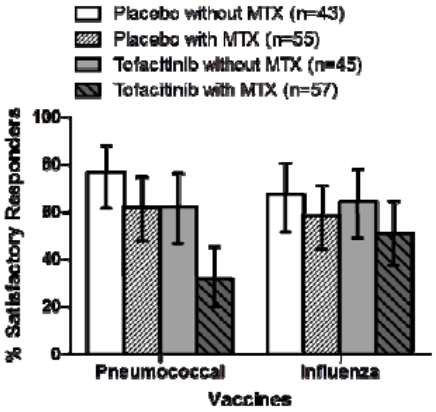
Correlation between LSC and ALC

Estimated Pearson correlation coefficients (R) values:

- CD3+ cells: 0.792-0.904
- CD4+ cells: 0.83-0.86
- CD8+ cells: 0.65-0.70
- NK cells: 0.27-0.48
- B cells: ~ 0.6

Vaccination responses

Figure 23 - Effects of Short Term Tofacitinib Treatment on the Percentage of Subjects Achieving Satisfactory Responses to Pneumococcal and Influenza Vaccines



Serious Infections (SIs)

SIs Incidence Rate/100 PY (95% CI)of tofacitinib in:

-RCTs (0-24 months): tofacitinib 5 mg BID: 2.71 (2.00, 3.58); placebo: 2.10 (0.77, 4.57)

-Study 1064: tofacitinib 5 mg BID: 5.26 (2.40, 9.98); Adalimumab: 1.68 (0.35, 4.90)

-Study 1069: tofacitinib 5 mg BID: 1.82 (0.91, 3.25); MTX: 1.87 (0.61, 4.36)

-All RA population: tofacitinib all doses: 2.74/100 PY (95% CI: 2.51, 2.99)

The most common serious infections in the tofacitinib 5 mg BID and 10 mg BID were pneumonia (24.5%, 18.5%), herpes zoster (9.1%, 7.2%), urinary tract infection (5.8%, 4.7%), and cellulitis (6.3%, 4.1%). Twenty-six (26) subjects died with a serious infection. Among these fatal events, infection was the initial event leading to death in 18 subjects.

The rate of serious infections was lower for monotherapy (6.42, 6.96, respectively) compared with co-administration with DMARD tofacitinib studies (13.50, 10.09, respectively).

Figure 24 - Meta-analysis of Incidence Rates for Serious Infections in Clinical Trials of Tofacitinib and Approved bDMARDs

Agent	No. of trials	Serious Infection Event, Incidence Rate/100 pt-yr (95% CI)	Patients (N)	Cumulative exposure (pt-yr)	Number of cases
Abatacept	11	3.04	5953	6070	202
Rituximab	8	3.72	2926	2687	81
Tocilizumab	13	5.45	5547	4522	199
Infliximab	11	6.11	4592	3555	202
Etanercept	17	4.06	7141	13037	591
Certolizumab pegol	5	7.59	3212	1339	102
Golimumab	6	5.31	2820	1648	79
Adalimumab	18	5.04	6570	7095	309
TNF inhibitors	57	4.90	26492	29429	1365
Tofacitinib, P123LTE all doses	18	2.74	6194	19229	527

2) Herpes Zoster (HZ)

HZ Incidence Rate/100 PY (95% CI)of tofacitinib in:

-RCTs (0-24 months): tofacitinib 5 mg BID: 3.43 (2.63, 4.41); placebo: 2.11 (0.77, 4.59)

-Study 1064: tofacitinib 5 mg BID: 3.52 (1.29, 7.66); Adalimumab: 2.81 (0.91, 6.57)

-Study 1069: tofacitinib 5 mg BID: 2.16 (1.15, 3.70); MTX: 0.76 (0.09, 2.73)

-All RA population: tofacitinib all doses: 3.91 (3.63, 4.21)

53/703 (7.5%) were serious. Most cases were mild (41.5%) or moderate (53.8%) and 73/703 (10.4%) were discontinued. The vast majority of subjects had involvement of a single dermatome and 2 had disease disseminated to the skin (of which one developed the infection following vaccine administration, Zostavax). There were no cases of visceral dissemination. The majority of cases recovered (see table below).

HZ live attenuated vaccine (Zostavax) study A3921237

Statistical Analysis of Fold Rise From Baseline (GMFR) in VZV-Specific IgG Levels at Visit 3 (Week 4) – EIAS

Placebo BID: 1.736 (80% CI: 1.546, 1.950)

Tofacitinib 5 mg BID: 2.105 (80% CI: 1.871, 2.369)

3) Opportunistic Infections (Excluding Tuberculosis)

OIs Incidence Rate/100 PY (95% CI)of tofacitinib in:

-RCTs (0-24 months): tofacitinib 5 mg BID: 0.11 (0.01, 0.40); placebo: 0.00 (0.00, 1.29)

-Study 1064: tofacitinib 5 mg BID: Adalimumab:0; placebo: 0.00

-Study 1069: tofacitinib 5 mg BID: 1 subject treated with tofacitinib 10 mg BID

-All RA population: tofacitinib all doses: 0.32 (0.24, 0.40)

Table 54 – Adjudicated opportunistic infections (All RA)

Type of Infection	Number of Subjects[a]
Viral	37
BK virus disease	1
Cytomegalovirus disease	7
Herpes zoster	29
Bacterial	3
Nocardiosis	1
Non-tuberculous mycobacteria	2
Fungal	22
Cryptococcosis	5
Pneumocystosis	5
Candidiasis	12

[a] One (1) subject experienced more than 1 OI.
OI=opportunistic infection, RA=rheumatoid arthritis

Outcomes of Subjects Who Developed Opportunistic Infections (All RA)

Outcomes	Number of Subjects (%)
Resolved	48 (78.7)
Ongoing	8 (13.1)
Unknown	1 (1.6)
Died	4 (6.6)

Source: P123LTE Table 972.1.11
RA=rheumatoid arthritis

4) Tubercolosis (TB)

TB Incidence Rate/100 PY (95% CI)of tofacitinib in:

-RCTs (0-24 months): tofacitinib 5 mg BID: 0.00 (0.00, 0.20); placebo: 0.00 (0.00, 1.29)

-Study 1064: tofacitinib 5 mg BID: 2 cases in tofacitinib group

-Study 1069: tofacitinib 5 mg BID: 2 cases in tofacitinib group

-All RA population: tofacitinib all doses: 0.19 (0.13, 0.26)

Most of these cases occurred in countries with intermediate or high TB burden. 19 of 36 (52.8%) of the TB cases were extrapulmonary. Most (83.3%) of these cases were considered serious and 58.3% of the cases were considered severe. None of the subjects who developed TB died while the diagnosis was still present.

5) All Malignancies (Excluding NMSC)

The most common malignancies observed in the RA clinical programme were non-melanoma skin cancer (NMSC), lung cancer, breast cancer, lymphoma, and melanoma.

	In the All RA population, the IRs (95% CI) per 100 pt-yr for the 5 mg BID, 10 mg BID dose groups and overall tofacitinib, respectively, and the age and gender adjusted standardized incidence (SIR),[a] respectively, were: • Malignancies (excluding NMSC): 1.01 (0.78, 1.27), 0.83 (0.68, 1.01), 0.89 (0.76, 1.04); SIR: 0.98 (95% CI: 0.84, 1.14) • Lymphoma: 0.09 (0.03, 0.19), 0.10 (0.06, 0.18), 0.10 (0.06, 0.15); SIR: 2.62 (95% CI: 1.58, 4.09) • Lung cancer: 0.20 (0.11, 0.34), 0.14 (0.09, 0.23), 0.17 (0.11, 0.23); SIR: 1.40 (95% CI: 0.96, 1.98) • Breast cancer: 0.19 (0.10, 0.35), 0.14 (0.07, 0.23), 0.16 (0.10, 0.23); SIR: 0.45 (95% CI: 0.29, 0.66) • Prostate cancer: 0.26 (0.05, 0.75), 0.32 (0.13, 0.67), 0.30 (0.14, 0.55); SIR: 0.72 (0.35, 1.33) • Melanoma: 0.04 (0.01, 0.13), 0.06 (0.03, 0.13), 0.06 (0.03, 0.10); SIR: 1.57 (95% CI: 0.79, 2.82)

Table 55 – Incidence rates per 100 pt-years, oservational literatura and standardized incidence ratios (SIRs) of malignancies

	Meta-analysis		
	Incidence Rate in Tofacitinib All RA (95% CI)	Pooled TNFi (95% CI)	Tofacitinib vs SEER SIR[a] (95% CI)
All Malignancies excl NMSC	0.89 (0.76, 1.04)	0.95 (0.81, 1.12)	0.98 (0.84,1.1)
Lung	0.17 (0.11, 0.23)	NA	1.40 (0.96, 1.98)
Breast	0.16 (0.10, 0.23)	NA	0.45 (0.29, 0.66)
Lymphoma	0.10 (0.06, 0.15)	NA	2.62 (1.58, 4.09)

	Meta-analysis		
	Incidence Rate in Tofacitinib All RA (95% CI)	Pooled TNFi (95% CI)	Tofacitinib vs SEER SIR[a] (95% CI)
Melanoma	0.06 (0.38, 0.10)	NA	1.57 (0.79,2.82)
NMSC[b]	0.62 (0.51, 0.74)	NA	

a. US population comparator
b. Data for NMSC are not collected in all registers; the approach for NMSC will be included in the submission
Abbreviations: NA = not available; TNF = tumor necrosis factor; EU = European union; ARTIS = Antirheumatic Therapies in Sweden; BIOBADASER = Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología; BSRBR = British Society of Rheumatology Biologics Register; CI = confidence interval; NMSC = non-melanoma skin cancer; RA = rheumatoid arthritis; RABBIT = Rheumatoid Arthritis Observational Biological Therapy Register of Germany; SEER = Surveillance, Epidemiology and End Results Program; SIR = standardised incidence ratio; US = United States
Source: Pfizer data on file

6) Effects of Tofacitinib on cardiovascular risk factors, MACE

Figure 24 - Total Cholesterol Levels (mg/dL) Over Time (RCTs, 0-24 Month)

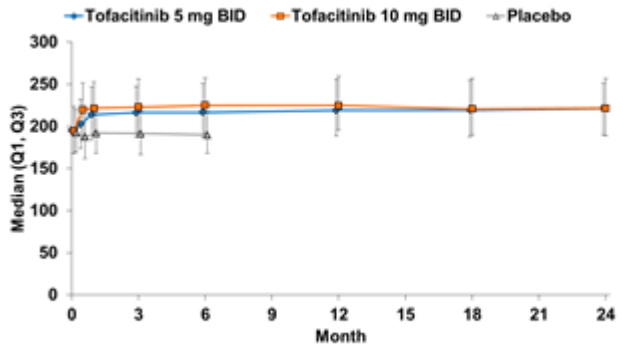
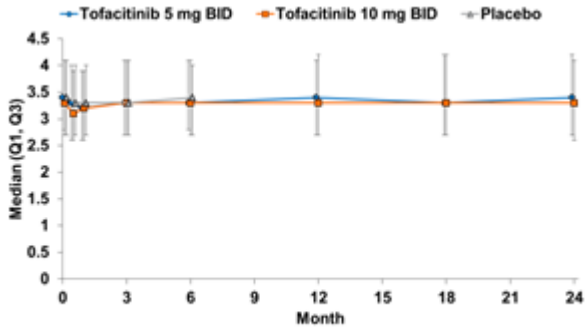


Figure 25 – Median Total Cholesterol / HDL-c Ratio over Time by visit (RCTs, 0-24 Month)



Major adverse cardiovascular events (MACE)

MACE Incidence Rate/100 PY (95% CI)of tofacitinib in:

-RCTs (0-24 months): tofacitinib 5 mg BID: 0.52 (0.24, 0.98) placebo: 0.49 (0.01, 2.75)
-All RA population: tofacitinib all doses: 0.39 (0.30, 0.49).

MACE was fatal in 10 subjects in 5 mg BID and in 9 subjects in 10 mg BID doses. Overall, almost all subjects had one or more risk factors for MACE.

7) Gastrointestinal (GI) perforations

GI perforation Incidence Rate/100 PY (95% CI)of tofacitinib in:

-RCTs (0-24 months): tofacitinib 5 mg BID: 0.00 (0.00, 0.20); placebo: 0.00 (0.00, 1.29)
-All RA population: tofacitinib all doses: 0.11 (0.07, 0.17)

All 22 subjects with events received concomitant therapy with NSAIDs or corticosteroids. Thirteen (13) subjects had a medical history of diverticulitis or diverticulosis and 2 additional subjects had a medical history of gastric ulcers. All events were reported as serious adverse events and all subjects discontinued participation in the respective study.

8) Hepatic safety

Table 56 - Number (%) of Subjects on Monotherapy with Confirmed Liver Function Test Values as Multiples of the Upper Limit of Normal (LTE)

	Normal Baseline n (%)			Abnormal Baseline n (%)		
	5 mg BID	**10 mg BID**	**All Tofa**	**5 mg BID**	**10 mg BID**	**All Tofa**
ALT (N)	**524**	**1106**	**1630**	**27**	**67**	**94**
≤1× ULN	428 (81.7)	912 (82.5)	1340 (82.2)	12 (44.4)	23 (34.3)	35 (37.2)
>1× ULN	96 (18.3)	194 (17.5)	290 (17.8)	15 (55.6)	44 (65.7)	59 (62.8)
≥2× ULN	21 (4.0)	42 (3.8)	63 (3.9)	3 (11.1)	13 (19.4)	16 (17.0)
≥3× ULN	6 (1.1)	16 (1.4)	22 (1.3)	2 (7.4)	4 (6.0)	6 (6.4)

	Normal Baseline n (%)			Abnormal Baseline n (%)		
	5 mg BID	**10 mg BID**	**All Tofa**	**5 mg BID**	**10 mg BID**	**All Tofa**
≥5× ULN	0	1 (<1.0)	1 (<1.0)	1 (3.7)	0	1 (1.1)
≥10× ULN	0	0	0	0	0	0

Table 57 - Number (%) of Subjects on Background DMARDs with Confirmed Liver Function Test Values as Multiples of the Upper Limit of Normal (LTE)

	Normal Baseline n (%)			Abnormal Baseline n (%)		
	5 mg BID	**10 mg BID**	**All Tofa**	**5 mg BID**	**10 mg BID**	**All Tofa**
ALT (N)	**825**	**1975**	**2800**	**72**	**198**	**270**
≤1× ULN	620 (75.2)	1505 (76.2)	2125 (75.9)	23 (31.9)	83 (41.9)	106 (39.3)
>1× ULN	205 (24.8)	470 (23.8)	675 (24.1)	49 (68.1)	115 (58.1)	164 (60.7)
≥2× ULN	47 (5.7)	83 (4.2)	130 (4.6)	13 (18.1)	26 (13.1)	39 (14.4)
≥3× ULN	15 (1.8)	31 (1.6)	46 (1.6)	8 (11.1)	9 (4.5)	17 (6.3)
≥5× ULN	4 (<1.0)	13 (<1.0)	17 (<1.0)	0	1 (<1.0)	1 (<1.0)
≥10× ULN	1 (<1.0)	5 (<1.0)	6 (<1.0)	0	0	0

No subject treated with tofacitinib met the definition of a Hy's Law case. One subject had increased transaminases and jaundice that worsened after tofacitinib discontinuation. The case was suspected to represent autoimmune hepatitis but the possibility of severe DILI cannot be excluded. Since this initial case, the adjudication process has not identified any additional severe DILI cases.

The most common reported event by PT was hepatic steatosis, which occurred in <1% of subjects in the RCTs and ~2 % of subjects in the LTE studies.

9) Interstitial lung disease (ILD)

ILD Incidence Rate/100 PY (95% CI)of tofacitinib in:

-RCTs (0-24 months): tofacitinib 5 mg BID: 0.11 (0.01, 0.40); placebo: 0.35 (0.01, 1.95)
-All RA population: tofacitinib all doses: 0.20 (0.14, 0.27)

Eighteen (18, 47.4%) of the adjudicated events of ILD were considered mild, 13 (34.2%) moderate and 7 (18.4%) were severe. One (1, 2.6%) subject died. Twenty-one (21, 55.3%) cases were still present at the time of the last evaluation, and 16 (42.1%) were considered resolved.

The incidence rate [per 100 PY (95% CI)] of ILD in Asia was higher [0.28 (0.15, 0.5)] than that of other regions, representing more than a third of the cases.

Laboratory findings

Hemoglobin

Table 58 - Number (%) of Subjects with Anaemia by CTC Grades (RCTs, 0-3 Month)

Treatment Group		GRADE 1 Haemoglobin <LLN to 10 g/dL	Grade 2 Haemoglobin <10.0 to 8.0 g/dL	Grade 3 Haemoglobin <8.0 to 6.5 g/dL	Grade 4 Haemoglobin <6.5 g/dL
	N	n (%)	n (%)	n (%)	n (%)
Tofa 5 mg BID	1823	406 (22.3%)	74 (4.1%)	2 (<1.0%)	0
Tofa 10 mg BID	1982	464 (23.4%)	80 (4.0%)	2 (<1.0%)	0
All Tofa	4603	1109 (24.1%)	198 (4.3%)	5 (<1.0%)	1 (<1.0%)
Placebo	1040	248 (23.8%)	57 (5.5%)	0	0

The sum of tofacitinib 5 mg BID and 10 mg BID doses may not equate to all doses. This is because there were subjects in the RCTs who received doses different than 5 mg BID and 10 mg BID or received placebo initially; these subjects are not counted in 5 mg BID or 10 mg BID but are counted in all doses.
The CTC grades are based on post-baseline lab values.
BID=twice daily, CTC=Common Terminology Criteria, LLN=Lower Limit of Normal, MTX=methotrexate, n=number of subjects with events, N=number of subjects evaluable, RCT=randomised controlled trial, Tofa=tofacitinib

LTE

The number of subjects who received tofacitinib and developed Grade 3 anemia (<8.0 to 6.5 g/dL) was 17 (<1%) or Grade 4 anemia (<6.5 g/dL) was 2 (<1%).

Creatine Kinase increase

During the RCTs (0-24 month) for subjects with baseline values within normal reference ranges receiving tofacitinib 5 mg BID, 10 mg BID and all subjects receiving tofacitinib, 2.5%, 5.0% and 3.8% of subjects, respectively, had at least 1 post-baseline CK value >3× ULN. The increases in CK in subjects taking tofacitinib were generally asymptomatic and mean values remained within normal reference ranges.

LTE

In the LTE population 9.4% of subjects with baseline values within normal reference ranges had at least one post-baseline CK value >3× ULN.

CK increase as AEs

Adverse events of CK increase were reported in 2.3% and 4.5% of subjects in tofacitinib 5 mg BID and 10 mg BID respectively, during the RCT studies with no further increase in the LTE studies.

In the All RA cohort, the majority of the events were assessed as non-serious (99.3%) and mild (72.1%) or moderate (25.6%) in severity. There were 3 subjects with reported serious events of CK increase, none of which were associated with rhabdomyolysis.

Serum Creatinine

The proportion of subjects with changes >33% from baseline in tofacitinib 5, 10 mg BID and placebo were 1.8%, 2.7%, and <1.0%, respectively, from 0 to 3 months. Less than 1.0% of any treatment group had confirmed increases of greater than 50% compared to baseline in serum creatinine.

AEs in the Acute Renal Failure SMQ: Within the first 3 months of study treatment, 4 (0.2%), 11 (0.5%) and 1 (0.1) subject, respectively, in the tofacitinib 5 mg BID, 10 mg BID and placebo group, were reported adverse event of increased creatinine by Acute Renal Failure SMQ

LTE Population

During long-term follow-up, 163 (3.3%) subjects reported adverse events of Blood creatinine increased 66 (1.4%) of whom discontinued the study; most events were reported by the investigator as mild or moderate in severity

Safety in special populations

Age

Table 59 - Number (%) of Subjects with Treatment-emergent Adverse Events by Age (RCTs)

Treatment	Tofacitinib 5 mg BID		Tofacitinib 10 mg BID	
Age Range	<65 years	≥65 years	<65 years	≥65 years
Subjects Evaluable for Adverse Events	1593	256	1735	289
Subjects With Adverse Events	1159 (72.8)	197 (77.0)	1263 (72.8)	232 (80.3)
Subjects With Serious Adverse Events	147 (9.2)	36 (14.1)	130 (7.5)	39 (13.5)
Subjects With Severe Adverse Events	144 (9.0)	27 (10.5)	121 (7.0)	34 (11.8)
Subjects Discontinued Due to Adverse Events	138 (8.7)	28 (10.9)	145 (8.4)	43 (14.9)

BID=twice daily, RCT=randomised controlled trial

Table 60 – Treatment-emergent adverse events by system organ class (SOC) in subjects who received tofacitinib 5mg BID by age strata (RCT population, 0-24 months)

Number (%) of Subjects With Adverse Events by SOC*	Tofacitinib 5 mg BID			
Age Group	**<65 years**	**65-74 years**	**75-84 years**	**≥85 years**
Subjects Evaluable for Adverse Events	**1593**	**213**	**42**	**1**
Number (%) of Subjects With Adverse Events	**1159 (72.8)**	**163 (76.5)**	**33 (78.6)**	**1 (100.0)**
Number (%) of Subjects Discontinued Due to Adverse Events	**138 (8.7)**	**19 (8.9)**	**8 (19.0)**	**1 (100.0)**
Blood and lymphatic system disorders	74 (4.6)	17 (8.0)	2 (4.8)	0
Cardiac disorders	51 (3.2)	8 (3.8)	2 (4.8)	0
Congenital, familial and genetic disorders	1 (0.1)	1 (0.5)	0	0
Ear and labyrinth disorders	26 (1.6)	10 (4.7)	1 (2.4)	0
Endocrine disorders	10 (0.6)	1 (0.5)	0	0
Eye disorders	52 (3.3)	13 (6.1)	1 (2.4)	0
Gastrointestinal disorders	396 (24.9)	58 (27.2)	12 (28.6)	0
General disorders and administration site conditions	138 (8.7)	17 (8.0)	4 (9.5)	0
Hepatobiliary disorders	22 (1.4)	6 (2.8)	0	1 (100.0)
Immune system disorders	18 (1.1)	1 (0.5)	1 (2.4)	0
Infections and infestations	641 (40.2)	89 (41.8)	17 (40.5)	0
Injury, poisoning and procedural complications	151 (9.5)	23 (10.8)	4 (9.5)	0
Investigations	249 (15.6)	23 (10.8)	5 (11.9)	0
Metabolism and nutritional disorders	104 (6.5)	14 (6.6)	1 (2.4)	0
Musculoskeletal and connective tissue disorders	265 (16.6)	38 (17.8)	11 (26.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	32 (2.0)	6 (2.8)	0	0
Nervous system disorders	201 (12.6)	27 (12.7)	5 (11.9)	0
Pregnancy, puerperium and perinatal conditions	0	0	0	0
Psychiatric disorders	71 (4.5)	2 (0.9)	2 (4.8)	0
Renal and urinary disorders	50 (3.1)	9 (4.2)	4 (9.5)	0
Reproductive system and breast disorders	45 (2.8)	1 (0.5)	0	0
Respiratory, thoracic and mediastinal disorders	136 (8.5)	19 (8.9)	5 (11.9)	0
Skin and subcutaneous tissue disorders	169 (10.6)	21 (9.9)	6 (14.3)	0
Social circumstances	1 (0.1)	0	0	0
Surgical and medical procedures	3 (0.2)	2 (0.9)	0	0
Vascular disorders	105 (6.6)	16 (7.5)	2 (4.8)	0

*Subjects were only counted once per treatment for each row
The randomised controlled trial (RCT) population includes Protocols A3921019, A3921025, A3921032, A3921035, A3921039, A3921040, A3921044 (2-year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year data), A3921073, and A3921129

Table 61 – Treatment-emergent adverse events by system organ class (SOC) in subjects who received tofacitinib 10mg BID by age strata (RCT population, 0-24 months)

Number (%) of Subjects With Adverse Events by SOC*	Tofacitinib 10 mg BID			
Age Group	**<65 years**	**65-74 years**	**75-84 years**	**≥85 years**
Subjects Evaluable for Adverse Events	**1735**	**257**	**31**	**1**
Number (%) of Subjects With Adverse Events	**1263 (72.8)**	**202 (78.6)**	**29 (93.5)**	**1 (100.0)**
Number (%) of Subjects Discontinued Due to Adverse Events	**145 (8.4)**	**35 (13.6)**	**8 (25.8)**	**0**
Blood and lymphatic system disorders	94 (5.4)	15 (5.8)	5 (16.1)	0
Cardiac disorders	43 (2.5)	9 (3.5)	4 (12.9)	0
Congenital, familial and genetic disorders	1 (0.1)	0	0	0
Ear and labyrinth disorders	30 (1.7)	6 (2.3)	1 (3.2)	0
Endocrine disorders	13 (0.7)	0	0	0
Eye disorders	43 (2.5)	13 (5.1)	1 (3.2)	0
Gastrointestinal disorders	417 (24.0)	69 (26.8)	13 (41.9)	0
General disorders and administration site conditions	170 (9.8)	26 (10.1)	4 (12.9)	1 (100.0)
Hepatobiliary disorders	44 (2.5)	5 (1.9)	0	0
Immune system disorders	8 (0.5)	2 (0.8)	0	0
Infections and infestations	749 (43.2)	106 (41.2)	18 (58.1)	1 (100.0)
Injury, poisoning and procedural complications	166 (9.6)	32 (12.5)	5 (16.1)	0
Investigations	310 (17.9)	47 (18.3)	7 (22.6)	0
Metabolism and nutritional disorders	152 (8.8)	20 (7.8)	6 (19.4)	1 (100.0)
Musculoskeletal and connective tissue disorders	262 (15.1)	52 (20.2)	8 (25.8)	1 (100.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	40 (2.3)	8 (3.1)	2 (6.5)	0
Nervous system disorders	219 (12.6)	24 (9.3)	7 (22.6)	0
Pregnancy, puerperium and perinatal conditions	4 (0.2)	0	0	0
Psychiatric disorders	70 (4.0)	10 (3.9)	4 (12.9)	0
Renal and urinary disorders	49 (2.8)	11 (4.3)	6 (19.4)	0
Reproductive system and breast disorders	52 (3.0)	4 (1.6)	0	0
Respiratory, thoracic and mediastinal disorders	145 (8.4)	28 (10.9)	7 (22.6)	0
Skin and subcutaneous tissue disorders	202 (11.6)	29 (11.3)	9 (29.0)	0
Social circumstances	1 (0.1)	0	0	0
Surgical and medical procedures	3 (0.2)	1 (0.4)	0	0
Vascular disorders	109 (6.3)	24 (9.3)	3 (9.7)	1 (100.0)

*Subjects were only counted once per treatment for each row
The randomised controlled trial (RCT) population includes Protocols A3921019, A3921025, A3921032, A3921035, A3921039, A3921040, A3921044 (2-year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year data), A3921073, and A3921129
Source: P2P3 Tables 1202b.1.1; 1202b.1.2; 1202b.1.3; 1202b.1.4
BID=twice daily; RCT=Randomised Clinical Trial; SOC=System Organ Class

Table 62 – Treatment-emergent adverse events by system organ class (SOC) in subjects who received placebo by age strata (RCT population, 0-24 months)

Number (%) of Subjects With Adverse Events by SOC*	Placebo			
Age Group	**<65 years**	**65-74 years**	**75-84 years**	**≥85 years**
Subjects Evaluable for Adverse Events	**916**	**143**	**20**	**0**
Number (%) of Subjects With Adverse Events	**497 (54.3)**	**69 (48.3)**	**14 (70.0)**	**NA**
Number (%) of Subjects Discontinued Due to Adverse Events	**47 (5.1)**	**10 (7.0)**	**1 (5.0)**	**NA**
Blood and lymphatic system disorders	24 (2.6)	1 (0.7)	0	NA
Cardiac disorders	10 (1.1)	0	0	NA
Congenital, familial and genetic disorders	0	0	0	NA
Ear and labyrinth disorders	6 (0.7)	0	0	NA
Endocrine disorders	2 (0.2)	0	0	NA
Eye disorders	10 (1.1)	2 (1.4)	1 (5.0)	NA
Gastrointestinal disorders	139 (15.2)	20 (14.0)	2 (10.0)	NA
General disorders and administration site conditions	51 (5.6)	11 (7.7)	2 (10.0)	NA
Hepatobiliary disorders	2 (0.2)	0	0	NA
Immune system disorders	2 (0.2)	0	0	NA
Infections and infestations	191 (20.9)	25 (17.5)	4 (20.0)	NA
Injury, poisoning and procedural complications	32 (3.5)	6 (4.2)	3 (15.0)	NA
Investigations	53 (5.8)	4 (2.8)	1 (5.0)	NA
Metabolism and nutritional disorders	20 (2.2)	2 (1.4)	2 (10.0)	NA
Musculoskeletal and connective tissue disorders	93 (10.2)	18 (12.6)	7 (35.0)	NA
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.4)	0	0	NA
Nervous system disorders	57 (6.2)	14 (9.8)	1 (5.0)	NA
Pregnancy, puerperium and perinatal conditions	1 (0.1)	0	0	NA
Psychiatric disorders	21 (2.3)	4 (2.8)	0	NA
Renal and urinary disorders	19 (2.1)	0	0	NA
Reproductive system and breast disorders	15 (1.6)	1 (0.7)	0	NA
Respiratory, thoracic and mediastinal disorders	40 (4.4)	5 (3.5)	2 (10.0)	NA
Skin and subcutaneous tissue disorders	59 (6.4)	7 (4.9)	2 (10.0)	NA
Social circumstances	0	0	0	NA
Surgical and medical procedures	1 (0.1)	0	0	NA
Vascular disorders	15 (1.6)	4 (2.8)	0	NA

*Subjects were only counted once per treatment for each row
The randomised controlled trial (RCT) population includes Protocols A3921019, A3921025, A3921032, A3921035, A3921039, A3921040, A3921044 (2-year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year data), A3921073, and A3921129
Source: P2P3 Tables 1202b.1.1; 1202b.1.2; 1202b.1.3; 1202b.1.4
NA=not applicable; RCT=Randomised Clinical Trial; SOC=System Organ Class

Table 63 – Treatment-emergent adverse events by system organ class (SOC) in subjects who received methotrexate by age strata (RCT population, 0-24 months)

Number (%) of Subjects With Adverse Events by SOC*	Methotrexate			
Age Group	**<65 years**	**65-74 years**	**75-84 years**	**≥85 years**
Subjects Evaluable for Adverse Events	**199**	**22**	**2**	**0**
Number (%) of Subjects With Adverse Events	**160 (80.4)**	**17 (77.3)**	**0**	**NA**
Number (%) of Subjects Discontinued Due to Adverse Events	**26 (13.1)**	**4 (18.2)**	**0**	**NA**
Blood and lymphatic system disorders	18 (9.0)	1 (4.5)	0	NA
Cardiac disorders	11 (5.5)	4 (18.2)	0	NA
Congenital, familial and genetic disorders	0	0	0	NA
Ear and labyrinth disorders	4 (2.0)	0	0	NA
Endocrine disorders	0	0	0	NA
Eye disorders	2 (1.0)	0	0	NA
Gastrointestinal disorders	77 (38.7)	9 (40.9)	0	NA
General disorders and administration site conditions	28 (14.1)	1 (4.5)	0	NA
Hepatobiliary disorders	8 (4.0)	0	0	NA
Immune system disorders	3 (1.5)	0	0	NA
Infections and infestations	65 (32.7)	9 (40.9)	0	NA
Injury, poisoning and procedural complications	14 (7.0)	2 (9.1)	0	NA
Investigations	40 (20.1)	1 (4.5)	0	NA
Metabolism and nutritional disorders	10 (5.0)	2 (9.1)	0	NA
Musculoskeletal and connective tissue disorders	40 (20.1)	6 (27.3)	0	NA
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.5)	1 (4.5)	0	NA
Nervous system disorders	27 (13.6)	2 (9.1)	0	NA
Pregnancy, puerperium and perinatal conditions	0	0	0	NA
Psychiatric disorders	11 (5.5)	0	0	NA
Renal and urinary disorders	6 (3.0)	0	0	NA
Reproductive system and breast disorders	5 (2.5)	0	0	NA
Respiratory, thoracic and mediastinal disorders	20 (10.1)	3 (13.6)	0	NA
Skin and subcutaneous tissue disorders	25 (12.6)	3 (13.6)	0	NA
Social circumstances	0	0	0	NA
Surgical and medical procedures	0	0	0	NA
Vascular disorders	10 (5.0)	1 (4.5)	0	NA

*Subjects were only counted once per treatment for each row
The randomised controlled trial (RCT) population includes Protocols A3921019, A3921025, A3921032, A3921035, A3921039, A3921040, A3921044 (2-year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year data), A3921073, and A3921129
Source: P2P3 Tables 1202b.1.1; 1202b.1.2; 1202b.1.3; 1202b.1.4

Table 64 - Treatment-Emergent Adverse Events by System Organ Class (SOC) in Subjects Who Received Adalimumab by Age Strata (RCT Population, 0-24 Months)

Number (%) of Subjects With Adverse Events by SOC*	Adalimumab			
Age Group	**<65 years**	**65-74 years**	**75-84 years**	**≥85 years**
Subjects Evaluable for Adverse Events	**219**	**35**	**3**	**0**
Number (%) of Subjects With Adverse Events	**148 (67.6)**	**26 (74.3)**	**2 (66.7)**	**NA**
Number (%) of Subjects Discontinued Due to Adverse Events	**22 (10.0)**	**5 (14.3)**	**0**	**NA**
Blood and lymphatic system disorders	2 (0.9)	0	0	NA
Cardiac disorders	3 (1.4)	3 (8.6)	0	NA
Congenital, familial and genetic disorders	0	0	0	NA
Ear and labyrinth disorders	4 (1.8)	3 (8.6)	0	NA
Endocrine disorders	0	0	0	NA
Eye disorders	4 (1.8)	1 (2.9)	0	NA
Gastrointestinal disorders	34 (15.5)	6 (17.1)	1 (33.3)	NA
General disorders and administration site conditions	23 (10.5)	2 (5.7)	1 (33.3)	NA
Hepatobiliary disorders	1 (0.5)	0	0	NA
Immune system disorders	1 (0.5)	0	0	NA
Infections and infestations	72 (32.9)	13 (37.1)	0	NA
Injury, poisoning and procedural complications	17 (7.8)	5 (14.3)	0	NA
Investigations	18 (8.2)	4 (11.4)	0	NA
Metabolism and nutritional disorders	11 (5.0)	2 (5.7)	0	NA
Musculoskeletal and connective tissue disorders	34 (15.5)	4 (11.4)	0	NA
Neoplasms benign, malignant and unspecified (incl	4 (1.8)	2 (5.7)	0	NA

Table 64 - Treatment-Emergent Adverse Events by System Organ Class (SOC) in Subjects Who Received Adalimumab by Age Strata (RCT Population, 0-24 Months)

cysts and polyps)				
Nervous system disorders	20 (9.1)	4 (11.4)	0	NA
Pregnancy, puerperium and perinatal conditions	0	0	0	NA
Psychiatric disorders	11 (5.0)	2 (5.7)	0	NA
Renal and urinary disorders	4 (1.8)	0	0	NA
Reproductive system and breast disorders	4 (1.8)	1 (2.9)	0	NA
Respiratory, thoracic and mediastinal disorders	16 (7.3)	2 (5.7)	0	NA
Skin and subcutaneous tissue disorders	25 (11.4)	5 (14.3)	0	NA
Social circumstances	0	0	0	NA
Surgical and medical procedures	0	0	0	NA
Vascular disorders	8 (3.7)	0	0	NA

*Subjects were only counted once per treatment for each row
The randomised controlled trial (RCT) population includes Protocols A3921019, A3921025, A3921032, A3921035, A3921039, A3921040, A3921044 (2-year data), A3921045, A3921046, A3921064, A3921068, A3921069 (2-year data), A3921073, and A3921129
NA=not applicable; RCT=Randomised Clinical Trial; SOC=System Organ Class

Table 65 - Treatment-Emergent Adverse Events by System Organ Class (SOC) in All Subjects Who Received Tofacitinib by Age Strata (LTE Population)

Number (%) of Subjects With Adverse Events by SOC*	All Tofacitinib Doses			
Age Group	**<65 years**	**65-74 years**	**75-84 years**	**≥85 years**
Subjects Evaluable for Adverse Events	**4096**	**682**	**86**	**3**
Number (%) of Subjects With Adverse Events	**3646 (89.0)**	**634 (93.0)**	**83 (96.5)**	**3 (100.0)**
Number (%) of Subjects Discontinued Due to Adverse Events	**810 (19.8)**	**237 (34.8)**	**33 (38.4)**	**2 (66.7)**
Being queried	17 (0.4)	1 (0.1)	0	0
Blood and lymphatic system disorders	459 (11.2)	91 (13.3)	11 (12.8)	1 (33.3)
Cardiac disorders	219 (5.3)	87 (12.8)	16 (18.6)	1 (33.3)
Congenital, familial and genetic disorders	18 (0.4)	6 (0.9)	2 (2.3)	0
Ear and labyrinth disorders	179 (4.4)	35 (5.1)	10 (11.6)	0
Endocrine disorders	90 (2.2)	11 (1.6)	1 (1.2)	0
Eye disorders	309 (7.5)	82 (12.0)	11 (12.8)	0
Gastrointestinal disorders	1297 (31.7)	246 (36.1)	30 (34.9)	2 (66.7)
General disorders and administration site conditions	526 (12.8)	134 (19.6)	25 (29.1)	2 (66.7)
Hepatobiliary disorders	215 (5.2)	40 (5.9)	5 (5.8)	0
Immune system disorders	93 (2.3)	14 (2.1)	3 (3.5)	0
Infections and infestations	2759 (67.4)	475 (69.6)	53 (61.6)	2 (66.7)
Injury, poisoning and procedural complications	872 (21.3)	183 (26.8)	23 (26.7)	2 (66.7)
Investigations	1166 (28.5)	218 (32.0)	23 (26.7)	2 (66.7)
Metabolism and nutritional disorders	630 (15.4)	121 (17.7)	14 (16.3)	0
Musculoskeletal and connective tissue disorders	1496 (36.5)	289 (42.4)	31 (36.0)	1 (33.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	347 (8.5)	100 (14.7)	20 (23.3)	1 (33.3)
Nervous system disorders	759 (18.5)	167 (24.5)	24 (27.9)	2 (66.7)
Pregnancy, puerperium and perinatal conditions	5 (0.1)	0	0	0
Psychiatric disorders	315 (7.7)	56 (8.2)	8 (9.3)	0
Renal and urinary disorders	295 (7.2)	88 (12.9)	17 (19.8)	0
Reproductive system and breast disorders	279 (6.8)	31 (4.5)	5 (5.8)	0
Respiratory, thoracic and mediastinal disorders	775 (18.9)	165 (24.2)	27 (31.4)	1 (33.3)
Skin and subcutaneous tissue disorders	735 (17.9)	160 (23.5)	24 (27.9)	1 (33.3)
Social circumstances	5 (0.1)	1 (0.1)	1 (1.2)	0
Surgical and medical procedures	6 (0.1)	0	0	0
Vascular disorders	542 (13.2)	135 (19.8)	24 (27.9)	0

*Subjects were only counted once per treatment for each row
The Long-Term Extension (LTE) population includes Protocols A3921024 and A3921041
LTE=long-term extension; SOC=System Organ Class

Gender

Males had a higher incidence of serious infections and MACE and a significantly higher risk of malignancies excluding NMSC and NMSC.

Paediatric population

The safety and efficacy of XELJANZ in children and adolescents less than 18 years of age have not yet been established.

Race

Subjects enrolled in Asia had the highest rate of serious infections and herpes zoster and OIs. As expected, countries with high TB incidence burden in their general population according to WHO were the countries with the highest incidence rate of TB. Only 1 case occurred among subjects enrolled in low burden countries.

Safety related to drug-drug interactions and other interactions

Concomitant Isionazid Therapy

In subjects with concomitant isoniazid, an increased potential for elevated transaminases or bilirubin when co-administered with tofacitinib, was reported.

Alcohol Use

During the Phase 3 studies, of 470 subjects using alcohol, 5 (1.1%) had confirmed measures of ALT >3 × ULN elevations in the tofacitinib 5 mg BID and 10 mg BID treatment groups. Of 1951 subjects not using alcohol, 20 (1.1%) had ALT >3× ULN elevations.

Discontinuation due to adverse events

RCT Population

Within the first 3 months of study participation, 2.3%, 2.0% and 1.6% of the subjects receiving tofacitinib 5 mg BID, 10 mg BID and placebo, respectively, discontinued from study due to adverse events. By SOC, adverse events of Infections and infestations represented the greatest proportion of discontinuations from study for tofacitinib 5 mg BID (0.8%) and 10 mg BID (1.0%), these rates were higher than that for placebo (0.5%).

All RA population

During long-term follow-up, adverse events in the Infections and infestations SOC were the most frequent reason for discontinuations from study for subjects receiving any dose of tofacitinib (8.5%).

By PT, pneumonia was the most common adverse events leading to discontinuations for subjects receiving any dose of tofacitinib (1.5%, the majority of which moderate to severe), followed by increase in blood creatinine (1.4%, the majority of which mild) and herpes zoster (0.8%, the majority of which moderate to severe).

Post marketing experience

A review of the types and reporting rates of post-marketing spontaneous/solicited /non-study literature adverse event reports supports the known safety profile of tofacitinib identified through the tofacitinib RA clinical development programme and no new safety signals were identified. All of the important identified and potential risks in the tofacitinib development programme will continue to be monitored through pharmacovigilance surveillance.

2.6.1. Discussion on clinical safety

The Grounds for Refusal related to the safety profile of tofacitinib were based on significant concerns and uncertainties surrounding the magnitude of the severe risks (including infections, malignancies, lymphoma, gastro-intestinal perforations).

With this new MAA the Applicant submitted further data in order to address I) the effects of tofacitinib on the immune system (dedicated immunology studies); ii) safety characterization (at 31 March 2015 data-cut off:, 19,405.8 patient-years (pt-yrs) of tofacitinib experience and up to 8 years of tofacitinib exposure); iii) Risk Characterization by comparison of incidence rates for key safety risks in EU RA patients exposed to tofacitinib and relevant second line comparators, using different approaches (i.e.peer-reviewed literature, meta-analyses, retrospective cohort studies and post marketing data).

Overall this comprehensive approach provides further characterization of the tofacitinib safety profile.

The patient exposure to tofacitinib (in all doses) is considered adequate both in terms of number of patients as well as duration of exposure to allow for a proper characterization of tofacitinib safety profile.

The exposure-adjusted IR for TEAEs in the RCT population over 24 months was higher in the placebo group compared to tofacitinib. This unexpected result could be due, at least in part, to the Applicant's choice to base comparison of safety profiles on exposure adjusted IRs, calculated on the basis of the assumption of a constant risk over time, for the placebo group after month 3. However, available data questions the constant risk assumption, as the majority of subjects treated with tofacitinib experienced TEAEs in the first 3 months. Moreover, the percentage of patient experiencing TEAEs has the limitation of not considering the different exposure in the placebo group, since non-responders subjects could move from placebo to tofacitinib arms at month 3. It is possible to express the TEAE incidence in 3-6 months considering the frequency of events on the population at risk at that time and not all the subjects that received placebo initially. A rough computation (it was supposed that half of the placebo group patients moved to treatment group at month 3 (as in in A3921064 study), showed that the frequency of TEAE events in 3-6 months period was 3.9% and approximately 10% in Tofacitinib arms. This implies that the apparent increased risk of IR for 0-24 months in placebo compared to treatment group, is an artefact due to the epidemiological measure choice and therefore the incidence rate of adverse events did not appear to be significantly lower for tofacitinib compared to placebo for the first 6 months.

Similar percentages of TEAEs were observed in the comparison of tofacitinib with adalimumab and MTX , although serious and severe TEAEs were more common in tofacitinib-treated patients compared to adalimumab. The overall TEAE frequency in adalimumab and MTX arms from studies 1064 and 1069 as compared to tofacitinib arms have also been provided based on the number of events. Overall, no substantial differences were noted comparing tofacitinib 5 mg BID groups to adalimumab and MTX groups, when TEAE frequencies are calculated based on the number of events or on the number of subjects with events. Serious and severe AEs are confirmed to be more common in tofacitinib 5 mg BID group compared to the adalimumab treatment group. From the comparison between TEAE IRs in the all RA population and the RCT population no time-dependent increase in the IR of TEAEs is apparent. The IRs were very different according the study phase. This is because studies of short duration provide the estimate of the risk of short-latency adverse events (mostly infections), while studies of long duration provide an estimate of the risk of long-latency (mostly cardiovascular disease) or infrequent events. As expected, the frequency of AEs over 24 months of therapy was lower when tofacitinib was used as monotherapy vs combination therapy with other DMARDs.

In the RCT population, the most common TEAEs in both tofacitinib and placebo groups were Infections and infestations, and Gastrointestinal disorders. The same was observed with adalimumab or MTX based on data from respective individual studies 1064 and 1069.

51 deaths occurred in the all RA population; 26 in the RCT population and 71 in LTE population. Infections, malignancies, and CV events were the most frequently reported reasons of death. No dose-dependent trend

was noted. Similar to TEAEs the IRs for deaths apparently do not increase over time, being lower in the All RA population than in the RCT population.

Of note an indirect comparison of all-cause mortality observed in tofacitinib-treated patients in the all RA population with EU registries, seems to not suggest an increase mortality for all cause in tofacitinib-treated subjects.

In the first 3-months of study treatment in the RCT population, similar proportion of patients (roughly 3%) treated with both tofacitinib dose and placebo experienced at least 1 SAE. The most common SAEs for tofacitinib treatment were in the Infections and Infestations SOC, the incidence of which was higher with tofacitinib than with placebo treatment. Among these, the most frequent SAEs with tofacitinib were pneumonia and herpes zoster compared with zero cases for both SAEs in the placebo group.

In the overall 24-month study period, a numerically higher IR of SAEs was observed in the placebo group compared to tofacitinib group. This is an unusual outcome, as already discussed; estimated IRs could have resulted in overestimation of AE rates in the placebo group if the events occurred mostly in first months of the treatment.

In comparison to adalimumab (study 1064) a higher percentage of tofacitinib treated subjects experienced at least 1 SAE. Infections and infestations were the most common SAEs observed with tofacitinib, mostly cellulitis, pneumonia and herpes zoster, which were experienced less frequently with adalimumab. Neoplasms were observed in 2% and 1.5% of tofacitinib 5 mg and 10 mg, respectively, and in 1% of Adalimumab group.

Similar percentages of SAEs were observed for tofacitinib and MTX, in study 1069, with infections and infestations (mainly pneumonia and gastroenteritis in the tofacitinib groups) most commonly recorded for both treatments arms. Neoplasms were observed with a slightly higher incidence in tofacitinib arms.

The incidence rate of SAEs apparently did not increase over time with long-term tofacitinib treatment (very similar IRs and CI intervals are reported between LTE and RCT population.

Across all pooled datasets discontinuation was mainly due to AEs and seemed to be not dose-related. The highest rate of discontinuation occurred in the first 6 months (22.98 100PY) with lower and relatively stable rates thereafter (ranging from 12.12-16.03).

Similar rates of discontinuation, mainly due to AEs, were observed in the comparison between tofacitinib and adalimumab treatments (study 1064), whereas, a higher incidence of discontinuations was recorded with MTX compared to both tofacitinib groups, in the monotherapy study (A321069). In tofacitinib-treated groups the most common drug-related reasons for discontinuations were adverse events, whereas lack of efficacy was the predominant reason in the MTX group. Of note, two deaths occurred in tofacitinib 5 mg BID arm and no deaths in tofacitinib 10 mg BID or the MTX group.

In view of the safety issues highlighted in the CHMP grounds for refusal of the previous MAA, in the present submission the Applicant focused the analysis of tofacitinib safety on the following AEs of special interest: Serious infections (SIs), Herpes zoster (HZ), Opportunistic infections (OIs) excluding tuberculosis (TB), TB, Malignancies, Major adverse cardiovascular events (MACE), Gastrointestinal (GI) perforations, Hepatic safety, Interstitial lung disease (ILD).

Serious infections (SIs)

New data, aimed at characterizing tofacitinib effects on neutrophil and lymphocytes count as well as correlation with SIs, were provided.

A reduction of the absolute neutrophil count (ANC) was observed at 3 months and stabilized thereafter without return to the baseline value. The decrease was of limited magnitude (median from baseline -0.8×10^3/mm^3), and reversible upon treatment discontinuation, with no subjects developing an ANC of <500 cells/mm^3 both in the RCT and LTE populations.

Most importantly, no association with clinical SIs (evaluation performed in a subgroup of subjects) was observed, giving reassurance on the clinical manageability of this important TEAE. Decrease in neutrophil count and neutropenia is retained as an important identified risk in the current RMP, instructions for dose adjustment have been included in section 4.2 of the SmPC and adequate information is provided as a warning in section 4.4 of the SmPC.

Absolute Lymphocytes count (ALC), was characterized by an initial transient increase followed by a progressive slow decrease below baseline values (up to -0.3×10^3 cell/mm^3 by 24 months) after 6 months of tofacitinib 5 mg BID (RCT population, 1064, 1069 and LTE studies).

A very limited number of subjects (approximately 1%) in the *All RA population* experienced severe decrease in ALC (ALC <500 cells/mm^3) and no patients in adalimumab and MTX arms had a confirmed ALC <500 cells/mm^3 in 1064 and 1069 studies, respectively. As expected, the majority of patients with ALC <500 cells/mm^3 were lymphopaenic at baseline (51% of subjects <1000 cells/mm^3). In addition, those who remained at ALC<500/mm^3 after tofacitinib withdrawal were mostly lymphopenic at baseline (<1000 cells/mm^3).

A potential association between different grades of lymphopenia as nadir values and clinical correlates suggested a higher IR of SIs, opportunistic infections, Herpes Zoster and Malignancies at the lowest ALC value (<500/mm^3). A full appreciation of the clinical correlates of tofacitinib-induced decrease in ALC is however prevented by the small number of patients with the lowest ALC values, as also reflected by the large CIs. The potential association of other grades of ALC with clinical correlates is further confirmed by a crude comparison showing a significant increase of SIs and OIs, as well as HZ IRs in the subgroup of patients with ALC ≥ 500 to <1000 cells/mm^3.

In order to manage decreases in ALC and the risk of serious and opportunistic infections, recommendations for treatment initiation and dose interruption have been included in section 4.2 of the SmPC. Patients with an ALC of less than 750 cells/mm3 should not initiate and/or should interrupt treatment with tofacitinib. This recommendation is supported by analyses in patients with an ALC nadir 500-750 versus 750-1000 cells/mm3 of exposure adjusted incidence rates (IR) for serious and opportunistic infections as well as zoster.

Results show that IR for serious infections was similar in the 750-1000 cells/mm3 category as compared to the ALC normal value (⩾1500 cells/mm3 category) but was meaningfully increased when ALC fell below 750 cells/mm3. However, the IRs for herpes zoster showed a trend to a progressively increase as ALC declines (of note, the lowest ALC category <0.5 cells/mm3 cannot be considered due to the very low number of patients with the event). An ALC threshold of < 750 cells/mm3, in the recommendations against treatment initiation and for treatment interruption, is on balance considered appropriate given that the Applicant has included a warning of ALC level below 1000 cells/mm3 among the risk factors which could increase the incidence of HZ (SmPC 4.4 section under viral reactivation). The SmPC includes additional warnings to

mitigate the risk of HZ as well as recommendations on appropriate consideration of prophylactic zoster vaccination.

Characterisation of lymphopenia

To address the CHMP concern on the lack of characterization of tofacitinib-induced lymphopenia, raised during the review of the previous MAA, and in response to the request to investigate the need of monitoring lymphocytes subset count (LSC) as a minimization measure, the Applicant performed a dedicated Immunological study of tofacitinib effect on lymphocytes subsets. Unfortunately, the study presents methodological flaws, limiting the interpretation of results, mainly due to the lack of comprehensive data (at baseline, during treatment, following treatment withdrawal) on lymphocyte subset profile in a unique, not preselected population.

LSC changes were observed mainly on some subsets, i.e. on NK cells and B cells, and although there is a biological plausibility for tofacitinib potential effect on LSC, due to the drug-induced inhibition of Jak, it may be difficult to conclude a causal correlation with tofacitinib treatment, also considering that the observed changes in LSC occurred in subjects already taking immunosuppressant therapies and affected by a disease characterized by impairment of the immune system. More importantly, the clinical correlate of some observed changes, like those between B cell count increase and lymphomas, are only suggested, but not ascertained or, in the case of the association between changes in CD4+ T cell count and OIs, even controversial.

In conclusion, LSC monitoring is not considered necessary or feasible on a routine basis.

Investigation of B cell functionality, in terms of immunoglobulin production during the first 6 months of tofacitinib treatment, showed only small decreases in IgG levels, although within normal ranges. Humoral response to pneumococcal polysaccharide vaccine (PPSV-23) appeared decreased during short and medium term combination therapy of tofacitinib compared to both MTX monotherapy and placebo, clearly indicating interactions between tofacitinib-MTX therapy and impairment of humoral response to PSV-23 vaccine at least up to 6 months of treatment.

No data on vaccination response were provided at longer time period. Consequently, the impact of long-term tofacitinib treatment on humoral response cannot be assessed.

Serious Infections

The presently submitted safety data derived from a longer time exposure in a larger number of subjects then those submitted in the previous MAA, confirms the higher IR of serious infections in the tofacitinib group as compared to both placebo and adalimumab.

Data in *the RCT population* showed a risk (calculated IRs ratio) of SIs 29% higher in tofacitinib 5mg BID compared to placebo. No increment of risk was observed in comparison to MTX treatment.

Of note, roughly 0,3% of tofacitinib-treated patients died from a serious infection and infection was the initial event leading to death in 18 subjects. However, the overall clinical impact of tofacitinib-induced SIs is at present not fully evaluable due to the lack of significant data, including total number of events, mean number per subject and outcome in the the *RCT population.* However, data provided seem to not show a particular trend in ALC decrease in subjects with fatal event compared to subjects who experienced a non-fatal serious infection event.

Partially reassuring data are derived from the indirect comparison of the risk of SIs linked to tofacitinib treatment with those reported for other DMARDs in the literature. However, several methodological

drawbacks have been identified in the performed literature search and meta-analysis, which prevent any sound conclusion on the results generated from this comparative exercise.

Herpes Zoster (HZ) infections

The issue of HZ infection was already raised within the grounds for refusal of the preceding MAA and the occurrence of Herpes zoster during tofacitinib treatment remains an important issue in consideration of the frequency of occurrence and the severity of the clinical manifestation. The incidence of HZ was generally higher in Tofacitinib compared to placebo and adalinumab, and it was higher when tofacitinib was given in combination with background DMARD(s) compared to monotherapy. Of note, IRs of 4.0 per 100 PY were estimated after short term exposure (0-6 months) to study drug, suggesting a causal relationship with tofacitinib-induced immunosuppression, and strong consistency with the trends observed for ALC decrease and occurrence of serious infections. Identified risk factors for HZ were age (⩾65 years), use of corticosteroids at baseline, diabetes and Asian race (IR of 8.10/100 PY in those from Japan and Korea; this information is now reflected in the SmPC through a dedicated warning). Of note, ALC < 1000 cells/mm3 was confirmed to be a risk factor for HZ.

Importantly, in the majority of subjects, HZ infections recovered and no HZ-related death was observed, suggesting that these infections are clinically manageable. Although HZ vaccination could be useful to reduce the risk of HZ infection, there is a risk of disseminated zoster infection if immunosuppressed patients are administered the live attenuated vaccine. Vaccination must take place therefore prior to initiation of tofacitinib and should be avoided if patients are immunocompromised from other prior immunosuppressant therapy.

In order to further investigate this issue, a new immunologic study (A3921237) aimed at testing specific immunogenicity and cellular immune response to the herpes zoster live attenuated vaccine (Zostavax) administration, has been included in the present MAA. Overall results for the first 3 months post vaccination show that both humoral and cellular response to the vaccine are not significantly impaired by tofacitinib. However, no information is available on persistence of zoster vaccine efficacy. In addition, one patient experienced dissemination of the vaccine strain of VZV, 16 days after vaccination (was varicella virus naïve and had no anti-varicella antibodies at baseline). A recommendation has been included in the SmPC to consider the risks and benefits of a live attenuated vaccine such as VZV vaccine at the patient level, in particular taking into account the state of immunosuppression and a need for confirmation of seropositivity to previous infection with VHZ without which there could be an unacceptable risk of disseminated vaccinia virus infection as a complication of live vaccination followed by tofacitinib initiation. The purpose of zoster vaccination is to provide a boost to existing host immunity but is considered too unsafe in patients who are VHZ naïve.

Opportunistic Infections (Excluding Tuberculosis)

OIs occurred in 9 subjects in the tofacitinib all doses *RCT population*, with an incidence rate of 0.20 per 100 PY and in 61 subjects in the *all RA population*. No cases of OI were observed with placebo and with adalimumab and MTX in studies 1064 and 1069, respectively. The most common OIs were herpes zoster involving more than 2 adjacent dermatomes and candidiasis. The majority of candidiasis were esophageal and one was an invasive candidiasis. The other OIs were CMV viremia/infections, cryptococcosis, Pneumocystis pneumonia, non-tubercolosus mycobacteria infections, nocardiosis, BK encephalitis. The spectrum of infections appears to be very similar to that found in AIDS suggesting an impaired cellular

immunity. However, as highlighted above, the potential correlation between nadir T cells and OIs remains controversial.

In more than half (54.1%) of patients OIs were considered serious and about half of patients with a OI discontinued from tofacitinib. The events resolved in the majority of subjects, however 4 patients (6.6%) died during the course of a OI. The occurrence of OIs is an important identified risk in the current RMP, and still raises concern given as it frequently requires discontinuation from study treatment. The need to reduce OIs further support the need to increase the lymphocyte cell threshold for considering treatment start as well as dose reduction and treatment discontinuation (see discussion on serious infections above).

A warning of increased risk of OIs in Asian geographic regions has been implemented, regardless of race, given that it may be related to local environmental reservoirs of opportunistic organisms.

Tubercolosis

The incidence rate of TB in the All RA population was consistent with that observed in the RCT population, and higher when tofacitinib was administered as concomitant therapy with DMARDs compared to monotherapy. A dose-response relationship is suggested by the data from both populations. Clinically, most of the cases were serious ad more than half were extrapulmonary. No apparent correlation of TB was observed with nadir lymphocytes counts. Most of the TB cases occurred in countries with high TB burden. TB is an important identified risk and the risk minimisation measures including the recommendation for latent TB screening in the SmPC are considered adequate.

Indirect comparisons of IRs of OIs and TB with tofacitinib and other DMARDs by SIR suggest a similar risk of SIs, however, data regarding OIs and TB cannot be considered conclusive since it is derived from too few events (as confirmed also by large CIs).

Malignancies

For a better risk characterization of malignancies, longer exposure data, a dedicated meta-analysis and EU registers data have been provided in the present MAA.

It should be consideedr that in RA patients some malignancies such as lymphoma, leukaemia, myeloma, lung cancer, non-melanoma skin cancer occur more frequently than in the general population and that immunosuppression could also contribute to increase malignancy rates.

The type of malignancies observed in the tofacitinib program were largely the same of those commonly reported in RA patients, and increased occurrence of a specific malignancy was not noted.

Data from the EU registries do not support an important increased risk of all malignancies (excluding NMSC) in the EU population following tofacitinib treatment. It is of note that slightly higher SIRs were reported for the global tofacitinib population as compared to the EU one, probably reflecting a different epidemiology of some cancers and related risk factors.

Among reported malignancies, lymphoma SIRs were higher in *the All RA* tofacitinib patient population as compared to the US general population and EU registries, however the incidence is comparable to that for biologic DMARDs.

Considering the mode of action of tofacitinib and the higher incidence of EBV-related lymphoproliferation in the 15-mg dose study in transplant patients, causality is not excluded. The relationship of the risk of lymphoma and the dose and duration of treatment of tofacitinib have been further explored together with the utility of testing for B cell monoclonality mainly in patients considered to be at high risk. However, data

provided suggests that tofacitinib treated patients are not at an increased risk of lymphoma relative to patients receiving bDMARDs and that tests for B cell monoclonality which are useful for lymphoma recurrence in oncology patients have limited predictive value for de novo disease.

Based on these data the Applicant has included malignancy as a potential risk in the RMP. This information is also reflected in section 4.4 of the SmPC. Also, long latency risks including malignancy and MACE will be evaluated in a post-authorization safety study.

LDL/MACE

Increase of LDL and related CV in the long term was an issue already raised during the review of the previous MAA.

In the present MAA the Applicant provided long term data up to 8 years including risk analyses.

In the RCT population, an increment from baseline in total, LDL and HDL cholesterol was observed from the first month of treatment with further small increments reported thereafter. Increments cholesterol levels appears to be dose-related, are reversible after withdrawal, and responsive to statins.

Increases in serum lipid levels following disease modifying therapies has been reported in the literature and discussed by the Applicant as a possible consequence of the suppression of systemic inflammation in RA subjects. Importantly, despite the increase in TC, the mean TC/HDL-c ratio did not change during tofacitinib treatment due to a simultaneous increase in HDL-c. In addition, no clear increase in MACE were observed over an adequate time period (up to >8 years). Rates from literature review of observational RA studies as well as data of EU registries seem consistent with those observed for tofacitinib in the RA population. Although data from tofacitinib RA program are quite reassuring, a relationship between lipid increase and CVD risk during tofacitinib treatment cannot be excluded, particularly in the RA population which is at higher risk of CVD compared to the general population. A recommendation for standard follow up of CV risk factors has been included in section 4.4 of the SmPC. The known increased risk for CV disorders in RA patients, often presenting one or more risk factors, is highlighted as well. Also, long latency risks including malignancy and MACE will be evaluated in a post-authorization safety study.

Gastrointestinal (GI) perforations

In the *all RA population* 22 subjects experienced GI perforation, IR for all tofacitinib doses consistent with that of the *RCT population*. Almost all events occurred in the tofacitinib 10 mg BID dose.

GI perforation was classified as potential risk in the RMP included the previous MAA. In the current MAA the Applicant proposes to reclassify GI to an important potential risk and to advise, in the 4.4 Section of the SmPC, for caution use of tofacitinib in subjects who may be at increased risk of GIP and for prompt clinical evaluation in case of new onset of abdominal signs and symptoms. This is agreed. However, concomitant use of corticosteroid and/or NSAIDs is now added among potential risk factors for GIP, as well.

GI perforation has been included in the RMP has an important potential risk and a warning has been included in section 4.4 of the SmPC, regarding for caution when using tofacitinib in subjects who may be at increased risk of GIP and for prompt clinical evaluation in case of new onset of abdominal signs and symptoms. Concomitant use of corticosteroid and/or NSAIDs is also added among potential risk factors for GIP.

Hepatic safety

The great majority of subjects experienced a transaminases increase ≤1× ULN. The proportions were lower for the 5mg tofanitinib dose compared to the 10 mg dose, and in the monotherapy setting.

Baseline values out of normal range as well as concomitant DMARD therapy are identified risk factors for transaminases increase.

These data raise some concerns given the expected frequent association of tofacitinib with MTX therapy. Transaminases increases and potential for drug induced liver injury has been included in the RMP as important identified risk. Routine monitoring of liver function tests, along with hematology, is recommended in the SmPC.

ILD

In the RCT population (0-24 Month), the ILD IR was similar in the tofacitinib 5 and 10 mg BID and lower compared to placebo group. However, an increase of events over time was observed. IDL events were moderate and severe in 34.2% and 18.4% of cases, respectively. Of note, a causal relation of ILD events with tofacitinib treatment may be difficult to establish due the frequent co-administration/history of use of MTX. A warning in relation to ILD is included in section 4.4.

Main Laboratory changes

Severe G3 anaemia was not frequently observed, even though RA patients could be prone to develop anaemic status. Decrease in haemoglobin levels and anaemia are include as an important identified risk in the RMP and modifications in the management of tofacitinib treatment based on haemoglobin values are included in section 4.2 of the SmPC.

Dose-related CPK increases were reported in the RCT and LTE population during the first 6-9 months of therapy, and appeared to reach a plateau thereafter. CPK increases were generally asymptomatic and mean values remained within normal reference ranges. CPK increase is included as an ADR in the tofacitinib SmPC.

A progressive small increment of serum creatinine from baseline was observed in tofacitinib groups of the RCT population up to 15 months after which reached a plateau and remained stable during LTE follow-up. Most events were mild or moderate in severity. The rise in creatinine levels was not associated with increased frequency of Acute Renal Failure.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Overall, the safety concerns highlighted in the previous MAA have been confirmed. However, data obtained from long term exposure as well as risk characterisation have now provided additional and more complete information leading to the clinical manageability of adverse events.

Following the better characterisation of the safety profile a substantial number of risk minimization measures have been implemented, including appropriate warnings in the product information, that will ensure the safe prescribing and use of tofacitinib.

An association between decline in absolute lymphocyte count (ALC) and incidence of serious infection has been demonstrated. The IR for serious infections was similar in the 750-1000 cells/mm3 category as compared to the ALC normal value (≥ 1500 cells/mm3 category) but was meaningfully increased when ALC fell below 750 cells/mm3. The IRs for herpes zoster show a trend to a progressive increase in HZ as ALC declines. Recommendations against treatment initiation and for treatment interruption where ALC is < 750

cells/mm3 is considered appropriate given that the Applicant has included a warning of ALC level below 1000 cells/mm3 among the risk factors which could increase the incidence of HZ (SmPC 4.4 section under viral reactivation). The SmPC includes additional warnings to mitigate the risk of HZ as well as recommendations on appropriate consideration of prophylactic zoster vaccination.

The safety data presented is considered by CHMP to be acceptable to support this application.

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important identified risks	Serious and other important infections
	Herpes zoster reactivation
	Decrease in neutrophil counts and neutropenia
	Decrease in lymphocyte counts and lymphopenia
	Decrease in haemoglobin levels and anaemia
	Lipid elevations and hyperlipidaemia
	Nonmelanoma skin cancer
	Transaminase elevation and potential for drug-induced liver injury
Important potential risks	Malignancy
	Cardiovascular risk
	Gastrointestinal perforation
	Interstitial lung disease
	Progressive multifocal leukoencephalopathy
	Increased immunosuppression when used in combination with biologic DMARDs and immunosuppressants including B lymphocyte depleting agents
	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
	Higher incidence and severity of adverse events in the elderly
Missing information	Effects on pregnancy and the foetus
	Use in breastfeeding
	Effect on vaccination efficacy and the use of live/attenuated vaccines
	Use in paediatric patients
	Use in RA patients with mild, moderate, or severe hepatic impairment
	Use in RA patients with moderate or severe renal impairment
	Use in patients with evidence of hepatitis B or hepatitis C infection
	Use in patients with elevated transaminases
	Use in patients with malignancy

CYP=cytochrome P450; DMARD=disease-modifying antirheumatic drug; JIA-juvenile idiopathic arthritis; MTX=methotrexate; RA=rheumatoid arthritis

Pharmacovigilance plan

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
Study A3921133: Phase 3B/4 randomized safety endpoint study of 2 doses of tofacitinib in comparison to a TNF inhibitor in subjects with RA 3	To continue to evaluate the 2 safety concerns that have a long latency period (ie, adjudicated MACE and adjudicated malignancies excluding NMSC of tofacitinib in patients with RA	The safety of tofacitinib at 2 doses versus adalimumab (co-primary endpoints include adjudicated MACEs and adjudicated malignancies excluding NMSC, secondary endpoint will evaluate adjudicated opportunistic OI events including TB and adjudicated hepatic events).	Started	Submission of the protocol by 09/2017 2020 (planned)
A lymphocyte subset sub-study within the LTE Study A3921024 3	To confirm the conclusions of analyses previously conducted between the risk of infections and lymphocyte subset levels. To evaluate whether monitoring of lymphocyte subset levels provides additional information beyond monitoring and discontinuation criteria based on total lymphocyte counts that could be used to mitigate the risk of infections	Serious infections, lymphopenia	Started	2017 (planned)

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned / Started)	Date for Submission of Final Study Report (Planned or Actual)
An EU-based survey for prescribers (RMM effectiveness assessment) 3	To assess prescribers' knowledge and understanding of the key risks associated with tofacitinib	Serious and other important infections, HZ reactivation, malignancies (including NMSC), changes in laboratory parameters, GI perforation, liver injury, increased immunosuppression when tofacitinib is used with other bDMARDS, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, primary viral infection following live vaccination, higher incidence and severity of adverse events in elderly patients, effects on pregnancy and the foetus, use in breastfeeding, effects on vaccination efficacy, use in populations with severe hepatic impairment	Planned	TBD
An EU-based drug utilization study using electronic health care records (RMM effectiveness assessment) 3	To assess prescription trends over time, as well as evaluate compliance with risk minimisation measures	Extent to which patient screening and laboratory monitoring recommendations and recommendations regarding limitations of use (and concurrent conditions, such as pregnancy, hepatic impairment, or concomitant use of bDMARDs) are followed, and off-label use.	Planned	TBD

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned /Started)	Date for Submission of Final Study Report (Planned or Actual)
Prospective, non-interventional comparative safety study embedded within the ARTIS registry 3	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	Serious infections,HZ reactivation, NMSC, malignancy, CV risk, GI perforation, PML, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of adverse events in elderly patients	Planned	TBD
Prospective, non-interventional comparative safety study embedded within the BSRBR registry 3	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	Serious infections, HZ reactivation, NMSC, malignancy, CV risk, GI perforation, PML, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of adverse events in elderly patients	Planned	TBD
Prospective, non-interventional comparative safety study embedded within the RABBIT registry 3	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	Serious infections, HZ reactivation, NMSC, malignancy, CV risk, GI perforation, PML, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of adverse events in elderly patients	Planned	TBD
Prospective, non-interventional comparative safety study embedded within the BIOBADASER registry 3	To further understand and characterise the safety profile of tofacitinib within the clinical practice setting	Serious infections, HZ reactivation, NMSC, malignancy, CV risk, GI perforation, PML, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of adverse events in elderly patients	Planned	TBD
Prospective, non-	To estimate the risk	Birth defects and other	Started	31 August

Study / Activity Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned /Started)	Date for Submission of Final Study Report (Planned or Actual)
interventional comparative pregnancy study embedded within the US OTIS registry 3	of birth defects and other adverse pregnancy outcomes occurring in offspring of patients exposed to tofacitinib during pregnancy, and to detect any increase in the prevalence or pattern of these outcomes among exposed pregnancies as compared with internally generated disease-matched and non-diseased control group.	adverse pregnancy outcomes		2018 (planned)
Prospective, non-interventional comparative safety study embedded within the Corrona registry (RA) 3	To provide additional longitudinal safety data regarding the use of tofacitinib in the US for RA patients.	Serious infections, HZ reactivation, malignancies, NMSC, cardiovascular events, PML, GI perforation, increased risk of adverse events in patients treated with tofacitinib in combination use of MTX, higher incidence and severity of adverse events in elderly patients	Started	TBD

ARTIS=Antirheumatic Therapies in Sweden; BID=twice daily; BIOBADASER=Registro Español de Acontecimientos Adversos de Terapias Biológicas en Enfermedades Reumáticas; BSRBR= British Society for Rheumatology Biologics Register; GI=gastrointestinal; ILD=interstitial lung disease; LTE=long term extension; MACE=major adverse cardiac event; MTX=methotrexate; NMSC=nonmelanoma skin cancer; OI=opportunistic infection; OTIS= Organization of Teratology Information Specialists; RA=rheumatoid arthritis; RABBIT=Rheumatoide Arthritis – Beobachtung der Biologika-Therapie; TB=tuberculosis; TBD=To be determined; TNF=tumour necrosis factor

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Serious and other important infections	Labelling	Development of an educational programme including additional communication to both

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
		patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Herpes zoster reactivation	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure, safety educational website).
Decrease in neutrophils counts and neutropenia	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Decrease in lymphocyte counts and lymphopenia	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Decrease in haemoglobin levels and anaemia	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Lipid elevations and hyperlipidaemia	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Nonmelanoma skin cancer	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure, safety educational website).
Transaminase elevation and potential for drug-induced liver injury	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Important Potential Risks		
Malignancy	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Cardiovascular risk	Labelling	None proposed
Gastrointestinal perforation	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Interstitial lung disease	Labelling	Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Progressive multifocal leukoencephalopathy	None proposed	None proposed
Increased immunosuppression when used in combination with biologic DMARDs and immunosuppressants including B lymphocyte depleting agents	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Increased risk of adverse events when tofacitinib is administered in combination with MTX	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure, safety educational website).
Primary viral infection following live vaccination	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors	Labelling	Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Prescriber Brochure, safety educational website).
Off-label use including children with JIA	Labelling	None proposed
Higher incidence and severity of adverse events in the elderly	Labelling	Development of an educational programme including additional communication to prescribers (including Prescriber Brochure, safety educational website).
Missing Information		
Effects on pregnancy and the foetus	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Use in breastfeeding	Labelling	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Effect on vaccination efficacy and the use of live/attenuated vaccines	Labelling	Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Use in paediatric patients	Labelling	None proposed
Use in RA patients with mild, moderate, or severe hepatic impairment	Labelling	Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure, safety educational website).
Use in RA patients with moderate or severe renal impairment	Labelling	None proposed
Use in patients with evidence of hepatitis B or C infections	Labelling	None proposed

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Use in patients with elevated transaminases	Labelling	None proposed
Use in patients with malignancy	Labelling	None proposed

CYP=cytochrome P450; DMARD=disease-modifying antirheumatic drug; JIA-juvenile idiopathic arthritis; MTX=methotrexate; RA=rheumatoid arthritis

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The CHMP, based on the available data, considers tofacitinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Jaqinus. The bridging report submitted by the applicant has been found acceptable.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Xeljanz (tofacitinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease that causes progressive damage to small and large joints (termed structural progression). RA is characterised by synovial inflammation and hyperplasia ("swelling"), autoantibody production, cartilage and bone destruction leading to deformity. It is also often associated with systemic complications arising from vasculitis together with cardiovascular and pulmonary complications.

3.1.2. Available therapies and unmet medical need

Available therapies for rheumatoid arthritis range from treatments that largely provide symptom relief, such as NSAIDs, to a number of conventional synthetic (cs) DMARDs, the folate antagonist methotrexate (MTX) being the cornerstone. Other csDMARDs can be used as alternatives or in combination with MTX. More recently, a range of biological therapies (bDMARDs) have been developed.

3.1.3. Main clinical studies

Six randomised, multi-centre, double-blind, parallel group Phase III studies evaluated the efficacy of tofacitinib in rheumatoid arthritis in a variety of settings relevant to 2nd, 3rd and also 1st line treatment.

	A3921032	A3921044	A3921045	A3921046	A3921064	A3921069
Study population	TNFi-IR	MTX-IR	DMARD-IR	DMARD-IR	MTX-IR	MTX-naïve[b]
No. of subjects randomized (treated)	399 (399)	800 (797)	611 (610)	795 (792)	717 (717)	958 (956)
Background treatment	MTX	MTX	None[a]	csDMARD(s)	MTX	None[a]
Prior MTX Treatment n(%)	393 (98.5)	796 (99.9)	518 (84.9)	668 (84.3)	717 (100)	65 (6.8)[b]
Key feature	TNFi-IR	X-Ray	Monotherapy	Various csDMARD	Adalimumab control	Monotherapy; X-Ray
Co-primary efficacy endpoints[c]	Month 3: • ACR20 • HAQ-DI • DAS28 <2.6[d]	Month 6: • ACR20 • mTSS • DAS28 <2.6[d] Month 3: • HAQ-DI	Month 3: • ACR20 • HAQ-DI • DAS28 <2.6[d]	Month 6: • ACR20 • DAS28 <2.6[d] Month 3: • HAQ-DI	Month 6: • ACR20 • DAS28 <2.6[d] Month 3: • HAQ-DI	Month 6: • mTSS • ACR70
Total study duration	6 months	2 years	6 months	1 year	1 year	2 years

3.2. Favourable effects

Structural progression

Study A3921069 (a monotherapy study in MTX naïve patients comparing with MTX alone) investigated structural progression. Clear superiority was demonstrated over MTX in the mean mTSS change from baseline at the primary endpoint of 6 months ($p = 0.0006$ and $p < 0.0001$ for 5 mg and 10 mg b.i.d. respectively). The slowing of progression was clinically relevant and in some, qualified as failure to progress (change in mTSS < 0.5 units). The mTSS endpoint was ranked second in the hierarchy but it can be formally considered, given that the preceding endpoint in the hierarchy (a stringent endpoint of ACR70 responder rate) had also been met ($p < 0.0001$ for both doses). The superiority over MTX for both endpoints was maintained out to 24 months. The study results are clearly positive. The structural outcome was supported by a range of composite secondary endpoints (including ACR20,50,70, DAS28 < 2.6, HAQ-DI and post hoc stringent measures including CDAI, SDAI), indicative of the benefit of tofacitinib on improving signs, symptoms and physical function of RA.

Benefit on signs, symptoms and physical function

Despite the failure to reveal benefit on structural progression for the tofacitinib combination with MTX in the second line setting, tofacitinib (at both doses) when in combination with MTX does demonstrate benefit on signs, symptoms and physical function in 2nd line (A3921044, A3921046 and A3921064) and 3rd line (A3921032) treatment settings. The post-hoc cross-study evaluation (which includes stringent composite scores of disease activity) supports a conclusion of clinical benefit on signs, symptoms and physical function in all the pivotal studies for tofacitinib even at 5 mg b.i.d..

Study A3921069 (tofacitinib as monotherapy in MTX naïve patients comparing with MTX alone) also demonstrated clear superiority over MTX ($p < 0.0001$ for both doses) in the endpoint of ACR70 responder rate, acknowledged as a stringent outcome measure of signs and symptoms. A range of additional composite secondary endpoints (including ACR20, 50, 70, DAS28 < 2.6, HAQ-DI and post hoc stringent measures including CDAI, SDAI) were also indicative of sustained benefit on signs, symptoms and physical function through to 24 months.

A second monotherapy study (A3921045) in second line patients (after DMARD washout) investigated signs and symptoms but did not evaluate structural progression as the co-primary endpoint was assessed at 3 months to minimise time on placebo. This study demonstrated a large difference from placebo in ACR20 responder rate (33.08 and 39.04% difference from placebo at 5 mg and 10 mg b.i.d, $p<0.0001$ for both) which was supported by the more stringent ACR50 and ACR70 measured as secondary endpoints. The second endpoint was also met (HAQ-DI $p<0.0001$ for both doses) but the third endpoint (DAS28-4(ESR) <2.6 responder rate) was not met at either dose (0.6193, 0.0728). This may have been an unrealistically stringent endpoint (disease “remission”) for this early time point and the ACR50 and ACR70 secondary endpoints are supportive of clinical relevance of the first two endpoints.

In summary, tofacitinib as monotherapy at a dose of 5 mg b.i.d. demonstrates benefit on signs, symptoms and physical function in both 1st (A3921069) and 2nd (A3921045) treatment line settings. In addition, tofacitinib in combination with MTX reveals benefit on signs, symptoms and physical function in 2nd (A3921044, A3921046 and A3921064) and 3rd line (A3921032) treatment settings.

3.3. Uncertainties and limitations about favourable effects

Structural progression

A second study investigated structural progression in 2nd line patients in the presence of background MTX (A3921044) which failed to demonstrate significant benefit of tofacitinib , compared with placebo (+MTX), on the endpoint of mTSS at 6 months with 5 mg b.i.d. (p=0.0792) although the 10 mg b.i.d. dose did just reach statistical significance (p=0.0376). Given that each endpoint in the hierarchy had to be met at both doses before proceeding to the next, the subsequent endpoints (HAQ-DI, DAS28-4(ESR) <2.6) could not be formally considered although both did reach statistical significance for both doses. The contribution of MTX to the suppression of acute phase reactant and hence to the decline in DAS28-4(ESR) score also needs to be taken into consideration, however.

The significant difference from placebo in change from baseline mTSS for the 10 mg dose was not maintained beyond 6 months. The radiographic progression data were subjected to linear extrapolation at the point of advancement from placebo to tofacitinib at 3 or 6 months, an accepted clinical trial design adaptation to the necessity for short placebo treatments in RA.

Study A3921044 was therefore somewhat different in its outcome from study A3921069 (a monotherapy study in MTX-naïve patients) which clearly demonstrated superior benefit compared to MTX on structural progression, which was maintained through to 24 months.

This apparent difference in structural preservation outcome may have been due to treatment line setting or the administration of tofacitinib in combination with MTX compared with tofacitinib as monotherapy. Two possibilities were considered: whether the MTX inadequately responsive population was less sensitive to revelation of structural benefit due to the likelihood of a smaller potentially responsive subset and a lower rate of structural progression in this treatment setting; or, the combination of MTX with tofacitinib could be exerting a negative effect on structural preservation, possibly due to a negative pharmacodynamic interaction.

Overall, the data points more towards the difference in structural outcome between these studies as due to differences in sensitivity of the respective populations to reveal a clear treatment benefit in structural benefit over a relatively short time period and that all patient populations are likely to have some capacity for structural preservation in response to tofacitinib. However, the question of whether MTX adds efficacy benefit, compared with tofacitinib as monotherapy, remains. This may be resolved when the ongoing head to head study of tofacitinib as monotherapy versus tofactinib in combination with MTX is available but is not considered to be required for approval. Given there is no clear signal of inferior efficacy with the MTX combination, and adequate warnings of risks associated with the combination are now in place, the current wording of the indication which gives precedence to the combination of tofacitinib with MTX is considered acceptable.

3.4. Unfavourable effects

There was substantial uncertainty about safety of tofacitinib at the time of the negative opinion in 2013 and in particular an absence of comparative data in relation to standard of care therapies for RA. Two of the three grounds for refusal were related to safety. Firstly, unresolved concerns over serious and opportunistic infections; and secondly, uncertainty about the overall safety profile including infections, malignancies, lymphoma, GI perforations, hepatic enzyme elevation, lipid elevation and cardiovascular risk.

The safety profile of tofacitinib while remaining complex and clinically challenging can now be considered sufficiently characterised for marketing authorisation.

Safety concerns have largely been confirmed by the updated safety analyses but the risks remain stable over time and are, with the exception of herpes zoster, largely in line with that of RA patients receiving bDMARD in the second line setting. The overall incidence of adverse events is also confirmed to be lower with the currently recommended maximum dose of 5 mg b.i.d. than the previously recommended maximum dose of 10 mg b.i.d. The risk of hepatotoxicity and infection is also lower with tofacitinib as monotherapy.

There is no increase in mortality for tofacitinib treated RA patients compared to RA patients as a whole. The only adverse event that occurs with higher frequency in tofacitinib plus MTX versus bDMARD (plus MTX) treated patients with RA is herpes zoster (IR 3.42 per 100 PYs) compared with bDMARD IR of 1-2 / 100PYs. The risk is lower with tofacitinib as monotherapy.

The option of prophylactic zoster vaccination is in place as a risk minimisation measure. A clinical study has confirmed efficacy and safety of zoster vaccination provided the vaccine is given a minimum of 2, preferably 4, weeks prior to commencement of tofacitinib and the patients are not varicella naïve. Without these precautions there is a risk of disseminated infection from the live vaccine and these have been strengthened by placing emphasis on serology to confirm varicella exposure and also taking account of the general state of health and immunocompetence of the patient.

Although the overall risk of malignancy is no higher than with bDMARD therapy, there is still uncertainty over this, given the long latency of many malignancies. Malignancy has been included as a potential risk in the RMP. This information is also reflected in section 4.4 of the SmPC. Also, long latency risks including malignancy and MACE will be evaluated in a post-authorization safety study.

Non-melanoma skin cancer is the commonest reported malignancy but this is overall no higher than in the RA population as a whole although the proportion of basal cell versus squamous skin cancer may appears to be altered, which will continue to be monitored through several post-authorisation safety studies. A warning has been included in section 4.4 of the SmPC highlighting that periodic skin examination is recommended for patients who are at increased risk for skin cancer.

The increase in lipids has been confirmed but the profile appears to be non-atherogenic. A warning has been included in section 4.4 of the SmpC regarding the assessment of lipid parameters. The incidence of GI perforations – 0.11 per 100PYs- is similar to in the overall RA population and mostly in association with predisposing factors such as steroid or NSAID use. The overall incidence of major cardiovascular events (MACE) is low (0.39 per 100 PYs).

Rises in hepatic transaminases are generally small and more likely to be above normal levels in combination with MTX.

The clinical immunology programme demonstrates a level of compromise to cell-mediated and humoral immunity that is consistent with the overall pattern of adverse events related to immunocompromise.

There is an increased incidence of herpes zoster but not of other adverse events in tofactinib treated bDMARD-IR, compared with MTX-IR patients (see SmPC section 4.4). Furthermore, with the exception of herpes zoster, adverse event rates from the tofacitinib clinical trial programme are consistent with those observed for bDMARD treated patients in the EU and US registries as well as in published RCTs. Uncertainties and limitations about unfavourable effects

Tofacitinib exhibits a complex safety profile as anticipated for a drug in this class, and there are still a number of uncertainties, particularly in relation to risks with a long latency including malignancy and major adverse cardiovascular events. Substantially increased risk minimisation measures, together with warnings and recommendations for precautionary measures in the product information, are now in place, allowing for a positive benefit risk balance of this product. Post-authorisation safety studies will also be conducted that will include evaluation of long latency adverse events.

3.5. Effects Table

Effects Table for Xeljanz (tofacitinib) indicated for rheumatoid arthritis.

This summarises outcomes from study A3921069 which is a key monotherapy study in MTX naïve patients that investigated structural progression; also study A3921045 monotherapy study in second line patients.

Effect	Short Description		Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
mTSS mean change from baseline 6 months	Measure of structural progression		Tofacitinib 5 mg b.i.d.	MTX	Strong evidence. P = 0.0006. Superiority over MTX. Maintained to 24 months. No confounding of data by linear extrapolation given there was no advancement from placebo.	
ACR70 response rate at 6 months	70% improvement in tender/swollen joint count plus patient and investigator global assessments; plus acute phase reactants		Tofacitinib 5 mg b.i.d.	MTX	Strong evidence. P < 0.0001 Considered a stringent endpoint	
ACR20 response at 3 months	20% improvement in tender / swollen joints etc		Tofactinib 5 mg b.i.d.	Placebo	Not so strong. Less stringent endpoint but 30% difference from placebo. P < 0.0001 . Short study so no radiographic data. Early benefit.	
Unfavourable Effects						
Herpes zoster	Usually single dermatome. Elderly and Asian population at higher risk Zostavax can be offered		Tofacitinib	bDMARD 1-2 / 100 PYs	Large safety database. Good certainty. Higher risk than bDMARDs Lower risk with 5 mg and monotherapy (IR 0.12 vs IR 0.45 per 100PY mono vs MTX combination	

Effect	Short Description	Treatment	Control	Uncertainties/ Strength of evidence	References
Serious incl opportunistic infections	Pneumonia, UTI, cellulitis, candidiasis	Tofacitinib	bDMARD	Large safety database. Overall similar incidence to bDMARDs . Lower risk of monotheraoy vs combination with MTX 0.12 vs 0.45 / 100PYs	
Transaminase	Small increase (median 1 IU/L for tofacitinib)	Tofacitinib	MTX	MTX alone has higher rate of >3xULN elevation than tof 5 mg (7.1% vs 3.1%)	

Abbreviations:

Notes:

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Tofacitinib at a dose of 5 mg b.i.d., whether as monotherapy or in combination with MTX, produces clinically relevant efficacy benefit on signs, symptoms and physical function in all treatment line settings. Tofactinib also has potential to slow progression of structural damage.

An apparent difference in structural preservation outcome, between the pivotal studies that investigated this, is likely due to differences in sensitivity of the respective populations (MTX naïve versus MTX inadequately responsive) to reveal a clear treatment benefit over a relatively short time period.

Tofacitinib administered in combination with MTX has comparable efficacy to tofacitinib administered as monotherapy, regardless of prognostic factors.

The question whether MTX adds efficacy benefit, compared with tofacitinib as monotherapy, remains, nonetheless. This may be resolved when the ongoing head to head study of tofacitinib as monotherapy versus tofactinib in combination with MTX is available but this is not considered to be necessary for approval of the marketing authorisation. Given there is no signal of inferior efficacy with the MTX combination, and adequate warnings are now included in the SmPC and the Risk Management Plan of a higher incidence of adverse events for the combination of Xeljanz with MTX, compared with Xeljanz as monotherapy, the current wording of the indication which gives precedence to the combination of tofacitinib with MTX is considered acceptable. The continuation of MTX, where tolerated, as background therapy is also preferred in clinical practice and therefore the indication, which prioritises the MTX combination over tofactinib as monotherapy, is in line with this. The specification of MTX as combination therapy is also aligned with the target population of MTX-IR patients.

The indication includes the statement that Xeljanz can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate which is considered to give the clinician sufficient scope to consider MTX as monotherapy.

3.6.2. Balance of benefits and risks

The initially proposed therapeutic indication specified MTX inadequately responsive (MTX-IR) patients as the principal target population. MTX is clearly stipulated in EU clinical practice guidance as first line anchor treatment for RA, unless the patient is ineligible to receive MTX or is intolerant. csDMARD can be offered as second line treatment to MTX-IR patients where there favourable prognostic factors (a biologic or targeted synthetic DMARD being recommended where there are unfavourable prognostic factors). It is therefore implicit that patients who are inadequately responsive to conventional synthetic DMARD (csDMARD) would also be those who are MTX-IR.

An MTX-IR patient population can also be considered to extend to biological DMARD inadequately responsive patients (bDMARD-IR). With regard to efficacy in the bDMARD inadequately responsive patient population, in a dedicated study that investigated such patients, there was a statistically significant difference between patients treated with tofacitinib 5 mg b.i.d compared to placebo in responder rates for attainment of DAS28-4(ESR) < 3.2 ("low disease activity") which is considered a sufficient efficacy target in this patient population. A detailed comparative safety evaluation was conducted in bDMARD-IR versus MTX-IR patients receiving tofacitinib and also with registry and published clinical trial data for patients receiving bDMARD therapy. The data overall confirm an increased incidence of herpes zoster but not of other adverse events in tofactinib treated bDMARD-IR, compared with MTX-IR patients. The incidence of HZ rises with increasing numbers of prior biologics. With the exception of herpes zoster, adverse event rates from the tofacitinib clinical trial programme are consistent with those observed for bDMARD treated patients in the EU and US registries as well as in published RCTs.

A positive benefit-risk is considered to exist in patients who have received prior biological therapy and who also have a sufficiently favourable risk profile that the risks do not outweigh the anticipated efficacy benefit. The warnings that have been implemented in the product information and Risk Management Plan of the increased risks in patients, who have received prior biological therapy, are considered to allow an informed benefit-risk evaluation for patients who have received prior biological therapy.

Therefore, a cross-reference to sections 4.4 and 4.5, where available data and appropriate warnings related to the use of tofacitinib in bDMARD-IR patients is available, has been included in section 4.1.

3.7. Conclusions

The overall B/R of Xeljanz is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Xeljanz is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to launch of Xeljanz in each Member State, the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The main objective of the programme is to increase awareness about the risks of the product, specifically in regards to serious infections, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy, gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities.

The MAH shall ensure that in each Member State where Xeljanz is marketed, all healthcare professionals and patients/carers who are expected to prescribe or use Xeljanz have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

- **The physician educational material** should contain:
    - The Summary of Product Characteristics
    - Guide for healthcare professionals
    - Prescriber checklist
    - Patient alert card
    - A reference to the website with the educational material and patient alert card

- **The Guide for healthcare professionals** shall contain the following key elements:
    - Relevant information of the safety concerns addressed by the aRMM (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable)
    - Details of the population at higher risk for the safety concern addressed by the aRMM (i.e. contraindications, risk factors, increased risk by interactions with certain medicine)
    - Details on how to minimise the safety concern addressed by the aRMM through appropriate monitoring and management (i.e. what to do, what not do, and who is most likely be impacted according to different scenarios, like when to limit or stop prescribing/ingestion, how to administer the medicine, when to increase/decrease the dosage according to laboratory measurements, signs and symptoms)
    - Key message to convey in patients counselling
    - Instructions on how to handle possible adverse events
    - Information about the BSRBR, ARTIS, RABBIT and BIODABASER registries and the importance of contributing to these

- **The Prescriber checklist** shall contain the following key messages:
    - Lists of tests to be conducted during the initial screening of the patient
    - Vaccination course to be completed before treatment
    - Relevant comorbidities for which caution is advised when Xeljanz is administered and conditions in which Xeljanz should not be administered
    - List of concomitant medications which are not compatible with treatment with Xeljanz
    - The need to discuss with the patients the risks associated with the use of Xeljanz, specifically in regards to infections, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy, gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities

- The need to monitor for any signs and symptoms and laboratory abnormalities for early identification of the abovementioned risks.

- **The patient alert card** shall contain the following key messages:
  - A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Xeljanz
  - That treatment with Xeljanz may increase the risk of infections and non-melanoma skin cancer
  - That patients should inform health professionals if they are planning to receive any vaccine or become pregnant
  - Signs or symptoms of the following safety concern and when to seek attention from a HCP: Infections, Herpes zoster reactivation, non-melanoma skin cancer, transaminase elevation and potential for drug induced liver injury, gastrointestinal perforation, interstitial lung disease, Increased immunosuppression when used in combination with biologic DMARDs and immunosuppressants including B lymphocyte depleting agents, Increased risk of adverse events when tofacitinib is administered in combination with MTX, Increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors, effects on pregnancy and foetus, use in breastfeeding, effect on vaccination efficacy and the use of live/attenuated vaccines.
  - Contact details of the prescriber

- **The centralised website** shall contain:
  - The educational material in digital format
  - The patient alert card in digital format

- **The patient information pack** should contain:
  - Patient information leaflet
  - The patient alert card

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers tofacitinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0013/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.