25 July 2013

EMA/CHMP/425279/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xeljanz

International non-proprietary name: tofacitinib

Procedure No. EMEA/H/C/002542/0000

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

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Product information

Name of the medicinal product:	Xeljanz
Applicant:	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ UNITED KINGDOM
Active substance:	tofacitinib citrate
International Nonproprietary Name:	tofacitinib
Pharmaco-therapeutic group (ATC Code):	Selective Immunosuppressants (L04AA29)
Therapeutic indication:	Treatment of rheumatoid arthritis in adult patients
Pharmaceutical form:	Film-coated tablet
Strengths:	5 mg and 10 mg
Route of administration:	Oral use
Packaging:	blister (alu/alu) and bottle (HDPE)
Package sizes:	56 tablets, 60 tablets and 180 tablets

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List of abbreviations

ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines)
AFB	Acid-fast bacilli
AFSSAPS	Agence Francaise de Securite Sanitaire des Produits de Sante (French Health Products Safety Agency)
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BA	Bioavailability
BE	Bioequivalence
BfARM	Bundesinstitut für Arzneimittel und Medizinprodukte (German: Federal Institute for Drugs and Medical Devices)
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CFB	Change from baseline
CHF	Congestive heart failure
CHOP	Cyclophosphamide-hydroxydaunorubicin-oncovin-prednisone
CI	Confidence interval
CIOMS	Council for International Organization of Medical Sciences
CK	Creatine kinase
CLt	Total clearance
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CORRONA	Consortium of Rheumatology Researchers of North America
COX	Cyclooxygenase
CrI	Credible intervals
CRP	C-reactive protein
CsA	Cyclosporine A
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CTA	Clinical Trial Application
CTD	Common Technical Document
CV	Cardiovascular
CV-SEAC	Cardiovascular Safety Endpoint Adjudication Committee
CYP3A4	Cytochrome P450 enzyme 3A4
CYP2C19	Cytochrome P450 enzyme 2C19
CYP450	Cytochrome P450
DAS28-4(ESR)	Disease activity score defined using 28 joint counts and erythrocyte sedimentation rate
DB	Double-blind
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DMARD	Disease modifying antirheumatic drug
DBP	Diastolic blood pressure
DSMB	Data Safety Monitoring Board
E-AER	Exposure-adjusted event rate
EBV	Epstein-Barr virus
EC_{50}	Concentration producing 50% of maximum effect
ECG	Electrocardiogram
eDISH	Evaluation of Drug Induced Serious Hepatotoxicity
EMA	European Medicines Agency
EOT	End of treatment
EPOCH	Etoposide-prednisone-vincristine-cyclophosphamide
ERPF	Effective renal plasma flow
ESRD	End stage renal disease
ESR	Erythrocyte sedimentation rate
EU	European Union
FDA	Food and Drug Administration
GBM	Glomerular basement membrane
GCP	Good clinical practice

GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HDL	High density lipoprotein
HLGT	High level group term
HLT	High level term
hOCT2	Human organic cationic transporter 2
HR	Hazard ratio
IC_{50}	Concentration producing 50% of inhibitory effect
ICH	International Committee on Harmonisation
ID	Identification number
IFN	Interferon
IL	Interleukin
ILD	Interstitial lung disease
INN	International Non-proprietary Name
INR	International normalized ratio
IR	Immediate release or Incidence rate
IV	Intravenous
JAK	Janus kinase
JNC7	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, 7th Report
LDH	Lactate dehydrogenase
LDL-c	Low density lipoprotein-cholesterol
LOV	Last observed visit
LPD	Lymphoproliferative disorder
LTE	Long-term extension studies
MALT	Mucosa-associated lymphoid tissue
MCavg	Time-averaged average concentration
MCID	Minimum clinically important difference
MCmax	Time-averaged maximum concentration
MCmin	Time-averaged minimum concentration
MCR	Mental Component Score
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MOA	Mechanism of Action
MPA-TLV	Sweden Medical Products Agency- Tandvårds- och läkemedelsförmånsverket
MRI	Magnetic resonance imaging
MSCT	Multislice computed tomography
mTSS	Modified total Sharp score
MTX	Methotrexate
NDA	New drug application
NMSC	Non-melanoma skin cancer
NOEL	No observed effect level
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
OGYI	Országos GNyógyszerészeti Intézet (National Institute of Pharmacy-Hungary)
OL	Open label
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
ONDQA	Office of New Drug Quality Assessment
OPC	Oral powder for constitution
OR	Odds ratio
P2MONO	Phase 2 studies with tofacitinib as monotherapy
P2MTX	Phase 2 studies with background methotrexate
P3DMARD	Phase 3 studies with background disease modifying antirheumatic drugs
P3MONO	Phase 3 studies with tofacitinib as monotherapy
P3MTX	Phase 3 studies with background methotrexate
PAH	Para-aminohippuric acid
PCS	Physical Component Score
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PI	Principal investigator
PID	Patient identification number
PK	Pharmacokinetic
PMAR	Population modeling analysis report
PML	Progressive multifocal leukoencephalopathy
PT	Preferred term
PTE	Probability of achieving a clinically meaningful target effect
PTLD	Posttransplant lymphoproliferative disease
PVAN	Polyomavirus-associated nephropathy
PYO	Patient years of observation
QbD	Quality by design
QD	Once daily

q2w	Once every 2 weeks
RA	Rheumatoid arthritis
RBC	Red blood cell
RCT	Randomized clinical trial
RMP	Risk management plan
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SCID	Severe combined immunodeficiency
SCLC	Small cell lung cancer
SCr	Serum creatinine
SEER	Surveillance Epidemiology and End Result
SIR	Standardized incidence ratio
SMQ	Standardized MedDRA query
SOC	System Organ Class
TB	Tuberculosis
TID	Three times per day
TNF	Tumor necrosis factor
TNFi	Tumor necrosis factor inhibitor
TyK	Tyrosine kinase
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
US	United States
USAN	United States adopted name
UTI	Urinary tract infection
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization
YLD	Years lived with disabilities

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Limited submitted on 27 October 2011 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 18 April 2011.

The applicant initially applied for the following indication: "Xeljanz is indicated with or without methotrexate (MTX) for treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have had an inadequate response or are intolerant to previous therapy with a disease-modifying anti-rheumatic drug (DMARD). Inhibition of the progression of joint damage has been shown in combination with MTX. Improvements in physical function have been shown with and without MTX.

The legal basis for this application refers to:

Article 8(3) of Directive No 2001/83/EC.

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 test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/162/2011 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/162/2011 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 citrate contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 22 January 2009. The Scientific Advice

pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Xeljanz has been given a Marketing Authorisation in the USA on 06 November 2012, Russia on 16 March 2013, Japan on 25 March 2013, Argentina 14 May 2013, United Arab Emirates 04 July 2013, Kuwait 09 July 2013, Switerzland 12 July 2013 and Colombia 26th July 2013.

1.2. Manufacturers

Manufacturer responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Mooswaldallee 1
D-79090 Freiburg
Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: Pierre Demolis Co-Rapporteur: Robert James Hemmings

CHMP Peer reviewer: Kristina Dunder

- The application was received by the EMA on 27 October 2011.
- The procedure started on 16 November 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 February 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 January 2012.
- During the meeting on 15 March 2012, 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 16 March 2012
- The applicant submitted the responses to the CHMP consolidated List of Questions on 13 September 2012.
- A triggered inspection was conducted at the site of the sponsor (Groton, USA) between 10 and 19 July 2012. The inspection report including the responses from the sponsor dated 17 September 2012 was circulated to the CHMP on 24 September 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 6 November 2012.
- During the CHMP meeting on 15 November 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 February 2013.
- During the CHMP meeting on 20 March 2013, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.

- During a meeting of an Expert group on 07 March 2013, experts were convened to address questions raised by the CHMP.
- During the meeting on 25 April 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Xeljanz.
- The applicant submitted written notice to the EMA on 30 April 2013 to request a re-examination of Xeljanz CHMP opinion of 25 July 2013.
- During its meeting on 27-30 May 2013, the CHMP appointed Hubert Leufkens as Rapporteur and Romaldas Mačiulaitis as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 13 June 2013 . The re-examination procedure started on 14 June 2013.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 5 July 2013. The Co Rapporteur's Assessment Report was circulated to all CHMP members on 4 July 2013 (Annex 8).
- During the PRAC meeting on 8-11 July 2013 the PRAC adopted the RMP advice and assessment overview following questions from the CHMP.
- During a meeting of an ad-hoc expert group on 15 July 2013, experts were convened to consider the grounds for re-examination.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 18 July 2013.
- During the CHMP meeting on 22 July 2013, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 22-25 July 2013, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

1.4. Steps taken for the re-examination procedure

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

Rapporteur: Hubert Leufkens Co-Rapporteur: Romaldas Mačiulaitis

- The applicant submitted written notice to the EMA on 30 April 2013 to request a re-examination of Xeljanz CHMP opinion of 25 July 2013.
- During its meeting on 27-30 May 2013, the CHMP appointed Hubert Leufkens as Rapporteur and Romaldas Mačiulaitis as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 13 June 2013. The re-examination procedure started on 14 June 2013.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 5 July 2013. The Co Rapporteur's Assessment Report was circulated to all CHMP members on 4 July 2013.
- During the PRAC meeting on 8-11 July 2013 the PRAC adopted the RMP advice and assessment overview following questions from the CHMP.
- During a meeting of an ad-hoc expert group on 15 July 2013, experts were convened to consider

the grounds for re-examination.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 18 July 2013.
- During the CHMP meeting on 22 July 2013, the detailed grounds for re-examination were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 22-25 July 2013, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application did not satisfy the criteria for authorisation and did not recommend the granting of the marketing authorisation.

2. Scientific discussion

2.1. Introduction

Problem statement

Rheumatoid arthritis (RA) is a chronic and systemic autoimmune disease characterized by synovial inflammation, cartilage and bone destructions with joints destruction leading to progressive disability, systemic features (including cardiovascular, pulmonary, psychological, and skeletal disorders), and sometimes auto-antibody production (rheumatoid factor and anti–citrullinated protein antibody [ACPA]). Joint destruction is believed to be irreversible resulting in significant morbidity.

Presentation of RA typically occurs between the ages of 20 to 40 years, with a female predominance on the order of 3:1. The World Health Organization (WHO) Global Burden of Disease 2004 update estimated the worldwide prevalence of RA at 23.7 million people, with 6.2 million in Europe and 4.6 million in the Americas (WHO, 2004). While there is considerable variation in the estimates of those affected by RA, the majority of studies from Northern European and North American areas estimate a prevalence of 0.5-1.0% and a mean annual incidence of 0.02-0.05%. Rheumatoid arthritis afflicts members of all ethnicities and races (WHO, 2004).

When compared with the general population, RA confers increased risk of mortality on the order of a 1.3 to 3-fold elevation. RA is associated with increased rates of cardiovascular illness, including myocardial infarction and heart failure, increase risk of lymphoma, higher rates of lung cancer. Some studies have noted more deaths attributed to infections, malignancies and cardiovascular disease.

Although RA pathogenesis is still not completely known, a central feature of RA is the dysregulation of innate and adaptive immunity with a relative imbalance in pro-inflammatory and anti-inflammatory cytokines, cytokine secretion playing a fundamental role in progression and chronicity of the disease.

The use of biologic agents targeting tumour necrosis factor alpha TNFα demonstrated the importance of this inflammatory cytokine in RA. However, only two thirds of patients respond to treatment suggesting the need for additional therapies. Targeting additional cytokines including IL-6, IL-23, IL-17 and the members of the common γ chain cytokines, including IL-7, IL-15 and IL-21, offer alternative targets for therapeutic efficacy. IL-6, IL-23 and the common γ chain cytokines signal via the JAK/STAT pathway. In addition, the induction, proliferation and maintenance of Th17 cells are supported by IL-6, IL-21 and IL-23. Therefore, small molecule inhibitors of the JAKs which mediate the signalling of many of these cytokines are potential therapies in RA.

In the last decade, the therapeutic landscape in RA disease has been consequently modified with the occurrence of biologic disease-modifying therapies, mainly driven by anti-TNF alpha inhibitors and other

biologic therapies with different mechanism of action. Nine biological DMARDs are approved in the treatment of RA patients, among them 8 are for the use in the second line, i.e. after failure to traditional DMARDs. In addition all these treatments have demonstrated their efficacy in the inhibition of progression of structural damage and have a specific claim in the wording of the indication.

EULAR treatment guidelines recommend initiating treatment with a non-biologic DMARD (usually MTX) as soon as a diagnosis (or a suspected diagnosis) of RA has been made. NSAIDs and/or low-dose glucocorticoids are typically continued while awaiting the effect of the newly started DMARD.

Patients who fail to benefit adequately from a particular treatment or are intolerant of the therapeutic agent, or who lose response to a therapeutic regimen may need to add or switch therapies. If the treatment target of remission or low disease activity is not achieved with the initial DMARD strategy, switching to, or addition of, another non biologic DMARD, or addition of a biologic DMARD is considered especially if the patient has poor prognostic factors. Addition of biologic DMARDs is typically reserved for those patients who have responded inadequately to at least one non-biologic DMARD. The most commonly and initially prescribed class of biologic DMARDs is a TNF inhibitor. If an inadequate response is observed to a treatment regimen including a biologic DMARD, a common response is to switch the biologic DMARD, either from one TNF inhibitor to another or to a biologic DMARD with a different mechanism of action.

About the product

Tofacitinib is a potent inhibitor of the Janus Kinase family, which inhibits preferentially JAK1/JAK3, and to a lesser extent JAK2 and TyK2. JAK pathways mediate the function of several cytokines, interferons and growth factors in the pathogenesis of rheumatoid arthritis. Small molecule inhibitors of the JAKs which mediate the signalling of many of pro-inflammatory cytokines are potential therapies in RA. Tofacitinib administered orally is a first in class immunosuppressant agent in rheumatoid arthritis.

The initially proposed indication read as follows: “Xeljanz is indicated with or without methotrexate (MTX) for treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have had an inadequate response or are intolerant to previous therapy with a disease-modifying anti-rheumatic drug (DMARD). Inhibition of the progression of joint damage has been shown in combination with MTX. Improvements in physical function have been shown with and without MTX”.

The oral tablet formulation of tofacitinib, dosed as 5 mg or 10 mg twice a day, has been developed for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease modifying antirheumatic drugs (DMARDs).

The recommended starting dose is 5 mg two times a day. Some patients may benefit from an increase to 10 mg two times a day based on clinical response. Tofacitinib may be taken with or without food.

Type of Application and aspects on development

The Community Marketing Authorisation Application (MAA) for tofacitinib is being submitted under the centralized procedure in accordance with Article 3(1) of Regulation (EC) No 726/2004: mandatory scope for a Centralised Marketing Authorisation; and Article 8(3) of Directive 2001/83/EC as amended.

In addition, in line with the Clarification for Applicants in the Centralised Procedure: Chemical (Non-Biological) Products, and the Notice to Applicants Vol 2A, Chapter 1, Annex 3, tofacitinib citrate, is considered a “new chemical active substance”.

Before starting the phase III RA programme, SA was sought from the EMA/CHMP (EMA/H/SA/1219/1/2008/III, Feb 2009). The following points were raised:

The CHMP suggested the inclusion of a TNFα failure study to obtain a 3rd line indication.

The dose rationale was accepted however concern was raised that the dose dependent increases in LDL were not considered with regards to the model on dose selection in which only changes in haemoglobin were factored.

Concerns were raised with regards to there being only 1 Phase III monotherapy study and 2 smaller Phase II studies which may be insufficient for the monotherapy indication.

The clinical database of approximately 2000 patients at that time was not considered large enough for the treatment of a common disease as a first in class immunosuppressant agent with adverse events on several organ systems, LDL levels and haematological parameters

During the procedure, the Applicant has changed the proposed invented name for tofacitinib from Jaqinus to Xeljanz.

2.2. Quality aspects

2.2.1. Introduction

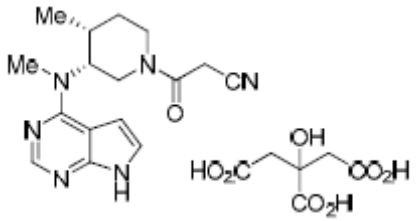
Xeljanz is presented as immediate-release film-coated tablets containing respectively 5mg and 10mg of tofacitinib (as tofacitinib citrate). The two strengths are dose proportional.

The 5mg strength is presented as white to off-white round immediate release film-coated tablets and the 10mg tablet is presented as blue round immediate release film-coated tablets. The tablets are debossed with 'Pfizer' on one side. The composition is described in section 6.1 of the SmPC.

The product is available in HDPE bottles with desiccant and polypropylene closures with induction seal liners or in Aluminium foil /PVC backed Aluminium foil unit dose blisters, as described in section 6.5 of the proposed SmPC.

2.2.2. Active Substance

The chemical name of tofacitinib citrate is 3-((3R,4R)-4-methyl-3-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)piperidin-1-yl)-3-oxopropanenitrile, 2-hydroxypropane-1,2,3-tricarboxylic acid. The molecular formula is C16H20N6O • C6H8O7 (citrate salt) and has the following chemical structure:



Tofacitinib citrate, the active substance of Xeljanz, is qualified as a New Active Substance (NAS) not described in any pharmacopoeia. Tofacitinib is a White to off white non hygroscopic powder that requires no special protection from humidity during handling, shipping, or storage.

The solubility of the active substance was evaluated in unbuffered water and standard aqueous buffers, its solubility is >28 mg/mL at pH 1.0, and decreases with the increase in pH (0.20 mg/mL at pH >8).

Tofacitinib contains two chiral centres at C3 and C4, and Pfizer production leads to one enantiomer with absolute configuration (R) for each C-3 and 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.

An extensive screening study to identify different potential polymorphic forms has demonstrated that only polymorph A can be consistently obtained in different circumstances studied. Therefore polymorphism has not been considered a critical quality attribute.

The applicant applied a quality by design approach during the development of the active substance. A quality target profile (QTP) of the active substance was established to deliver a safe, efficacious, and stable drug product, and serve as the basis for process design and development.

Manufacture

Tofacitinib is supplied by one active substance manufacturer. The synthesis of tofacitinib citrate consists of four chemical transformations in three steps.

A design space was applied for the manufacturing process of the active substance. The drug substance CQAs and the control strategy have been adequately described. The design space was established with lab scale batches.

The Applicant has presented detailed data on risk assessment, criticality of each step of manufacture using Failure Mode Effect and Criticality Analysis (FMECA) and high resolution design of experiments for steps 1 and 2 and sub-steps 3 along with their statistical analyses. The conclusions of these design of experiments (DoEs) generally support the ranges of critical process parameters (CPPs) and non (CPPs) described. The manufacturing process is well described and adequate in-process controls are applied during the synthesis.

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 is observed.

Taking into account the experience gained during manufacture of clinical and registration stability batches and the process validation results, it can be considered that the DS has been verified at commercial scale when operating within the NORs. The applicant was invited to provide a verification protocol to describe how changes outside the NORs will be managed. The submitted protocol is a generic protocol from Pfizer with few tofacitinib citrate specific points. However, since it has been already approved in a previous application from Pfizer, the protocol is accepted at this stage.

The impurity profile of the active substance is another critical attribute that has been established on the basis of batch history and those impurities typically present in manufactured batches; the grounds of qualification of two of them were not provided in the dossier. Furthermore, characterisation of impurities PF-05198213 and PF-05211077 was not complete, as results of the Ames test, performed in accordance with ICH Q3A, were not provided in the dossier.

Specification

The active substance specification includes tests for appearance (visual), identification (FTIR), particle size (wet dispersion laser diffraction), assay (LC), assay of citric acid (LC), impurities (LC), residue on

ignition (USP), heavy metals (USP), residual solvents (GC) and water content (KF). The test methods have been adequately described and validated in line with the ICH guidelines.

Analytical methods are in general sufficiently described and validated. However, lack of a simple test for chiral identity correlated to the chiral purity of the substance was not addressed.

Batch analysis data have been provided for 26 batches of the active substance, 13 of these batches were manufactured with the process as proposed for marketing. These batches were used for development, stability studies and for the manufacture of drug product used in clinical studies and for commercial purposes. The results are within the specifications and consistent from batch to batch.

Stability

Stability information for three batches of tofacitinib drug substance, packaged in double polyethylene (PE) bags stored in polyethylene (PE) drums has been completed according to ICH Q1A (R2) guidelines through 24 months at the long term condition of 25°C/60% RH and 6 months at the accelerated condition of 40°C/75% RH. Parameters that have been monitored were appearance, assay by HPLC, purity by HPLC, water content, chiral purity by HPLC, and microbial contamination; the acceptance criteria applied were those applied at release. These stability studies include batches of tofacitinib citrate manufactured by the process representative of the commercial process.

Stress studies were conducted on samples of tofacitinib drug substance to confirm the suitability and specificity of the assay and purity method to separate and identify potential degradation products of the drug substance. Tofacitinb citrate is found to be sensitive to oxidative, acidic and alkaline conditions. The LC assay and purity method were shown to be stability indicating and peak purity demonstrated via diode-array and mass spectral detection

Photostability testing

A photostability study was carried out for one batch of the active substance according to the ICH Guideline Q1B with Option 2.

Samples were tested for appearance, purity, chiral purity and water content.

No significant changes in the appearance, assay, impurities, water content or chiral purity were observed in the exposed sample. Based on these results, it can be concluded that tofacitinib citrate is not a light sensitive substance.

In the post-approval stability protocol, inclusion of assay testing at all-time points and commitment to continue long term stability study for the proposed retest period was presented. This is considered acceptable.

Based on ICH long term and accelerated stability data provided for lots obtained by the commercial process, a retest period of 36 months can be accorded without any precaution of storage when tofacitinib citrate is packed in double PE bags and placed in a secondary container such as HDPE or fiber drum.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim was to develop immediate-release film-coated tablets containing respectively 5mg and 10mg tofacitinib suitable for oral administration, twice daily, in adult patients. The formulation development was based on a quality by design (QbD) approach: a Quality Target Product Profile (QTPP) was defined, and the drug product quality attributes were identified.

After a comprehensive screening of various potential counter ions of tofacitinib, the crystalline citrate salt of tofacitinib was selected for the commercial product because it is chemically and physically stable under different storage and process conditions. It is highly soluble across physiologically relevant pH and has suitable pharmaceutical properties for development. Tofacitinib citrate is classified a BCS class 3 compound (high solubility and low permeability) and the particle size is not expected to have significant effect on dissolution. However, drug substance particle size could influence uniformity of dosage units, because of the low drug load in the tablet formulation. To assess the impact of drug substance particle size on uniformity of dosage units, a QbD approach, that includes mathematical modelling, development scale multivariate experiments, and pilot/production scale manufacturing experience, was followed.

The excipients of this drug product were selected based on the results of excipient compatibility studies, chemical compatibility studies with the active substance, and based on the excipient's mechanical properties. Based on the results, the following excipients have been selected for the final tablet core: microcrystalline cellulose (diluent), lactose monohydrate (diluent), croscarmellose sodium (disintegrant), and magnesium stearate (lubricant). These excipients are typically used for dry granulation. The selection of the commercial film-coating system was based on compatibility of the various coating materials with the drug substance. A hydroxypropyl methylcellulose (HPMC) based coating system with aluminium lake pigments was selected. All excipients comply with the Ph.Eur., including all ingredients of the commercial film coating. The list of excipients is included in section 6.1 of the SmPC. The tablets used in phase 2 and 3 clinical studies have the same qualitative composition as the tablets proposed for marketing, with the exception of the lactose grade used and the film coating. A bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed 10 mg commercial formulation. Since the 5mg and 10mg commercial tablets use a common blend and share the same manufacturing process, the equivalence between the 5mg and 10mg registration tablets was demonstrated by the in vitro dissolution test.

During pharmaceutical development, process understanding was achieved through iterative risk assessments, through Failure Mode Effect and Criticality Analysis tools (FMECA), univariate studies, multivariate studies and modelling tools, in order to establish linkages between inputs (raw materials, process parameters), intermediate attributes and finished product CQAs. The main factors identified as CQAs for drug product were the uniformity of dosage units, the tablet water content and the level of degradants. A control strategy has been put in place to ensure that all CQAs and the associated QTPP requirements are achieved and that the manufacturing process is robust and reproducible.

The proposed primary packaging is HDPE bottles with desiccant and polypropylene closures with induction seal liners or in Aluminium foil / PVC backed Aluminium foil unit dose blisters. The material complies with Ph. Eur. requirements and it is adequate to support the stability and use of the product.

Adventitious agents

It is confirmed that the lactose monohydrate used in the manufacture of Xeljanz 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. The magnesium stearate used in Xeljanz is of vegetable origin. The manufacturers of the packaging components have provided certification letters attesting to their safety with respect to minimizing the risk of transmitting animal spongiform encephalopathy agents. No excipients derived from human origin have been used.

Manufacture of the product

The Xeljanz tablets are manufactured by a conventional dry granulation process that includes the steps: blending, milling, intragranular lubrication, dry granulation, extragranular lubrication, compression, film coating. The process is considered to be a standard manufacturing process. A detailed description of the commercial manufacturing process and process flow chart have been provided. The manufacturing process development was based on a quality by design (QbD) approach and designed to consistently meet the quality attributes, which were derived from the drug product profile.

Among the multivariate studies performed, four designs of experiments (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 (DS) covering mainly dry granulation and milling parameters.

Validation of the manufacturing process is planned to be completed on the first three production batches manufactured at the claimed commercial site. This is acceptable considering that an extensive development has been carried out to increase process knowledge. Moreover, a product-specific DS verification protocol at commercial has been provided. The additional tests proposed for each attribute/parameter movement within Design Space, as a function of drug product quality attributes that can be impacted, are found adequate.

Product specification

The finished product release specifications include appropriate tests for: appearance (visual), identification (NIR, UV, LC), assay (NIR or LC), uniformity of dosage units (NIR or LC), impurities (LC), disintegration (Ph.Eur), water content (KF) and microbial limits (Ph.Eur). Batch analysis results have been provided for the clinical batches and the registration batches. Results show that the registration batches manufactured at the commercial site comply with the specifications

The specifications have been justified taking into account the CQAs and control strategy that is in place.

Near Infra-Red Spectroscopy has been proposed for assay, uniformity of dosage unit and identity testing of the drug product. The overall approach for the development of the NIR method is acceptable. However, at the time of the Opinion clarifications were still needed on the scope of the NIR method and model updates. Moreover a Post approval change management protocol should have been submitted to address the overall strategy and type of variation to be submitted to allow the switch from the HPLC to the NIR method for release purposes.

Due to use of large sample size in the frame of NIR procedures, large sample size (≥100 units tested) acceptance criteria (in line with Ph. Eu. 2.9.47 requirements) are proposed for content uniformity.

Disintegration test is proposed to be used in lieu of dissolution test which is justified based on the demonstrated relationship between the two attributes. Moreover, a skip testing for disintegration has also been accepted based on the increased process understanding and the proposed design space.

Stability of the product

Stability data for three batches of each strength have been provided. The batches were stored under long term conditions (25°C/60% RH and 30°C/75% RH) for up to 12 months and under accelerated conditions (40ºC/75%RH) for up to 6 months, according to the ICH guidelines. The stability batches were

manufactured at greater than 10% of commercial scale, using commercial equipment at the proposed Pfizer commercial manufacturing site. The stability batches were packaged in the primary packaging proposed for marketing.

The stability samples were evaluated for appearance, assay and degradation products, as well as water content, dissolution, chiral purity, disintegration and microbiological quality. The analytical procedures used were stability indicating. The stress testing studies have shown an increase in the drug product related degradants with increasing exposure to humidity. For this reason high density polyethylene bottles (HDPE) with desiccant, and aluminium foil blisters with aluminium foil backing were selected for the commercial tablets to provide protection from moisture during long term storage. The data from the registration stability study demonstrate that there are no trends observed in any of the measured parameters under the storage conditions as defined in the proposed SmPC.

The applicant used a bracketing design for the stability studies of the HDPE bottle packages to cover the range of tablets per bottle and different bottle sizes for the two strengths. The other packaging (foil/foil blister) on the other hand, was tested for all lots and tablet strengths.

In addition, the photostability of one batch for each strength was evaluated in accordance with ICH guideline Q1B. The exposed samples were tested for appearance, assay, degradation products, water content, dissolution, disintegration and hardness.

Furthermore an open dish study was carried out on one 5 mg and one 10 mg tablet batch. Samples were removed from the package and stored in an open dish at 30°C/75% RH and tested after 2 and 4 weeks. Samples were tested for appearance, assay and degradation products, water content, dissolution and disintegration.

Based on the stability data a shelf-life of 24 months could be accepted without any special storage condition as stated in the SmPC.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Xeljanz is presented as immediate-release film-coated tablets containing respectively 5mg and 10mg of tofacitinib (as tofacitinib citrate) as the active substance.

Tofacitinib citrate, the active substance of Xeljanz, is qualified as a New Active Substance (NAS) not described in any pharmacopoeia. A Quality by Design (QbD) approach was used for the manufacturing process development of drug substance and the pharmaceutical development of drug product. Extensive development studies have thus been conducted for both.

For the active substance the impurity profile is a critical attribute that has been established on the basis of batch history and those impurities typically present in manufactured batches; the grounds of qualification of two of them are still to be provided in the dossier. Furthermore, characterisation of impurities PF-05198213 and PF-05211077 was not complete, as results of the Ames test, performed in accordance with ICH Q3A, were not provided in the dossier.

Analytical methods are in general sufficiently described and validated. However, a simple test for chiral identity correlated to the chiral purity of the substance was not provided.

The applicant defined a design space for the finish product covering mainly the dry granulation and milling steps.

The applicant has applied for Real Time Release Testing for the drug product using Near Infra-Red (NIR) method for assay, uniformity of dosage unit and identity. At the time of the opinion there were unresolved

issues relating to the method description and post approval maintenance of the proposed NIR method. The management protocols are not finalised.

The benefit-risk assessment for authorisation of this product should take into account the limitations listed above.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The medicinal product Xeljanz is formulated as immediate-release film-coated tablets containing respectively 5mg and 10mg of Tofacitinib. The two strengths are dose proportional. Drug substance (citrate salt) is introduced at a level of approx. 4% w/w within the total finished tablet. Excipients are compendial (except for the coating) and are conventional for this kind of pharmaceutical formulation. A fixed quantitative composition is set. The tablets are manufactured by a dry granulation process.

The applicant defines a design space (DS) for the drug substance and for the finish product (covering mainly dry granulating and milling parameters).

The change management protocols are still pending and will be amended when all the remaining issues are solved. At the time of the opinion the CHMP has identified the following non-resolved Quality issues:

1. Specificity of the chromatographic method used for impurities of CP-759,970 has been shown towards diastereoisomers PF-04897847and CP-910, 607/9. The specificity towards PF-06298154 is not demonstrated.
2. Absence of an Ames test on impurities PF-05198213 and PF-05211077 according to ICH Q3A and also a timetable for the conduct and reporting of these studies.
3. Absence of chiral identification test justified by historical data. The Applicant's reference to the ICH Q11 is acknowledged however the reference made is about enantiomeric purity/impurity and not about chiral identification. In addition, ICH Q6A, decision tree 5 recommends in all cases a chiral identity test; this could be a simple test such as specific optical rotation correlated to the chiral impurity for the S, S isomer. Alternatively, the available chiral impurity test can be included in the specifications however performed on a non routine basis.
4. The method descriptions / scopes have been completed with some NIR parameters, however all the requested parameters have not been included in the method scope.
    a. The identity of the apparatus was not specified as described in the methods validation
    b. The chemometric model is defined as « PLS » only; the key parameters of the PLS model as well as the software are not described in the scope.
    c. The items described under method scope cannot be considered "example". They are registered as part of method description.
5. Post approval change management protocol to address the overall protocol (approximate number of batches, paired results, acceptance criteria…) and type of variation to be submitted when the switch from HPLC methods to NIR methods should have been envisaged.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases. In kinase assays, tofacitinib inhibited JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibited signalling by heterodimers containing JAK1 or JAK3 (JAK1/3) with functional selectivity over JAK2 homodimer signalling.

The primary pharmacodynamic testing program of tofacitinib included in vitro assays to determine potency and selectivity. To determine potency of tofacitinib in a cellular setting dependent on combinations of JAKs, a series of cell-based assays were performed and included inhibition of enzymatic activity, cell activity based on transcription factor readout, on protein readout, and cell activity in human whole blood based on signal transducer and activation of transcription (STAT) phosphorylation. To evaluate in vivo pharmacodynamics, rodent models of arthritis (murine CIA and rat AIA) were assessed by clinical and histopathological measures of disease progression. Additional studies measuring reverse cholesterol transport were performed to elucidate the effects of CP-690,550 on total plasma cholesterol that were observed in AIA rats. Secondary pharmacodynamics was assessed by evaluating the binding potency of CP-690,550 on a broad panel of receptors, ion channels, and enzymes. In addition, the effect of CP-690,550 on circulating reticulocytes in the context of erythropoietin (EPO) administration was evaluated in cynomolgus monkeys. Safety pharmacology studies were conducted *in vitro* and *in vivo* (rats, mice, and monkeys) to assess potential effects on the CVS, respiratory, and CNS endpoints.

The pharmacokinetics program was designed to characterize the absorption, distribution, metabolism and excretion properties and the pharmacokinetic-pharmacodynamic (PK-PD) relationship to support nonclinical safety evaluation and relevance to humans. The single-dose pharmacokinetics of tofacitinib was assessed in rats, dogs and monkeys following oral and intravenous administration. Pharmacokinetic/toxicokinetic data of tofacitinib were obtained following acute and repeated-dose administration. The toxicity of CP-690,550 was evaluated in mice, rats, rabbits and monkeys. *In vitro* and *in vivo* genetic toxicology studies were conducted to assess the genotoxic potential of CP-690,550. Chronic toxicology assessment was conducted in rats and monkeys. Carcinogenicity was assessed in a 6-month rasH2 transgenic mouse and conventional 2-year rat carcinogenicity studies. Additionally, investigative mechanistic studies, reproductive studies in rats and rabbits, in vitro and in vivo phototoxicity studies, and other local tolerance studies have been conducted.

Scientific advice on the toxico-pharmacological development for tofacitinib was received from the EMA/CHMP.

All studies were conducted in compliance with GLP except for some preliminary dose-setting studies and other non-pivotal studies which were not conducted in compliance with these regulations.

2.3.2. Pharmacology

Tofacitinib is a potent inhibitor of the Janus Kinase family, which inhibits preferentially JAK1/JAK3, and to a lesser extent JAK2 and TyK2. JAK pathways mediate the function of several cytokines, interferons and growth factors in the pathogenesis of rheumatoid arthritis.

The Janus kinase (JAK) family, including JAK1, JAK2, JAK3 and tyrosine kinase 2 (TyK2), is a group of cytoplasmic tyrosine kinases that mediate signal transduction via interactions with type I and type II cytokine receptors. Of the four family members, JAK1, JAK2 and TyK2 are ubiquitously expressed and

associated with numerous types of cytokine receptors. 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. Upon binding of the cytokine to its receptor, the associated JAKs are activated and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the signal transducer and activator of transcription (STAT) family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) of transcription factors. The STATs are then phosphorylated by the co-localized JAKs, which stabilizes homo- or heterodimeric STAT complexes that translocate to the nucleus where they bind to specific gene promoters to activate transcription of a range of target genes. 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. 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.

Primary pharmacodynamic studies

In vitro studies

Table 1: Summary of *in vitro* primary pharmacodynamics studies

Type of Study, Study reference	Test system	Main findings
IC50 Determination D08AI0333	0.01–1000 nM	**IC50** JAK1 = 3.2 ± 1.4 nM JAK2= 4.1 ± 0.4 nM JAK3 = 1.6 ± 0.2 nM TYK2 = 34 ± 6 nM
Inhibition Characterization D08AI0334	0–6 nM tofacitinib 8.2–2000 ìM MgATP	Tofacitinib is an ATP competitive inhibitor. **Ki** JAK1: 0.68 ± 0.12 nM JAK2: 0.97 ± 0.03 nM JAK3: 0.24 ± 0.03 nM TYK2: 4.4 ± 0.3 nM
Kinase Selectivity CP-690550_20Apr11_083053	0.01–30000 nM	Tofacitinib selectively inhibited JAK3. All other kinases tested had IC50s >1 µM with the majority measuring >10 µM.
IL-23/IL-21 Dependent STAT3 Phosphorylation CP-690550/19Jan10/142305	Kit 225 T cells alone or in presence of human whole blood 0.1–30000 nM	**Tofacinitib inhibited JAK1/JAK3-dependent STAT3 phosphorylation by IL21.** *Kit 225 cells* IC50 = 0.006 ± 0.001 µM *Kit 225 cell in HWB* IC50 = 0.020 ± 0.003 µM **Tofacinitib inhibited JAK2/TyK2-dependent STAT3 phosphorylation by IL23.** *Kit 225 cells* IC50 = 0.040 ± 0.015 µM *Kit 225 cell in HWB* IC50 = 0.102 ±0.017 µM
IL-2/IL-12 Signaling in Human PBMCs D08AI0337	Human PBMCs and Whole Blood 0.076–40000 nM	**IL-2 (JAK1/3) induced IFNγ** PBMC: IC50 = 26 ± 2 nM HWB: IC50 = 34 ± 6 nM **IL-12 (JAK2/TYK2) induced IFNγ** PBMC: IC50 = 129 ± 36 nM HWB: IC50 = 501 ± 197 nM

STAT Phosphorylation in Human Whole Blood D08AI0338	Human Whole Blood 1–200000 nM	**CD8+ T lymphocytes** IL-15 (JAK1/3)-dependent STAT5 phosphorylation IC50 = 56 ± 6 nM **CD14+ monocytes** IL-6 (JAK1/2)-dependent STAT3 phosphorylation IC50 = 406 ± 68 nM GM-CSF (JAK2)-dependent STAT5 phosphorylation IC50 = 1377 ± 185 nM
STAT Phosphorylation in Human Whole Blood CP-690550/11Dec09/113015	Human Whole Blood 1–200000 nM	**CD3+ T lymphocytes** JAK1/3-driven signaling in response to γc-cytokines (IL-2, IL- 4, IL-7, IL-15 or IL-21); IC50 = 28± 5 nM, 50 ± 6 nM, 38 ± 9 nM, 30 ± 5 nM and 25 ± 6 nM, respectively. JAK1/TyK2-dependent IL-10 and IFNα stimulated STAT phosphorylation; IC50 = 141 ± 36 nM and 44 ±4 nM, respectively. JAK1/JAK2-dependent – IL-6 IC50 = 54 ±7 nM and 367 ± 49 nM for STAT1 and STAT3 phosphorylation, respectively. **CD20+ B lymphocytes** IL-4 induced STAT6 phosphorylation; IC50 = 111 ± 48 nM **CD14+ monocytes** JAK1/2-dependent IFNγ stimulated STAT phosphorylation with an IC50 of 178 ± 38 nM, and JAK1/TyK2-dependent STAT phosphorylation by IFNα and IL-10 with IC50 of 148 ± 41 nM and 206 ± 46 nM, respectively

In vivo studies

Table 2: Summary of *in vivo* primary pharmacodynamics studies

Study Type/ Study Reference	Species (Strain)	Dose (mg/kg) Route	Results
In Vivo Potency and Selectivity in Mouse Whole Blood CP-690550/22Dec09/153609	DBA1 Mouse Whole Blood (5 – 15 Males)	Single Dose 0.15–50 mg/kg	**CD8+ T lymphocytes** *IL-15 (JAK1/3) STAT5* EC50 = 273 ± 47 nM *IL-6 JAK1/2 STAT1* EC50 = 470 ± 84 nM and **CD11b+ Monocytes** *GM-CSF STAT5* EC50 = 6656 ± 1243 nM
Prophylactic Treatment CP-690550/15Jan10/ 151443	Mouse CIA Model (10 – 15 Males)	1.5–15 mg/kg/day SC infusion 0.5–100 mg/kg BID or QD orally (Days 22-56)	Tofacinitib significantly reduced the incidence and severity of arthritis symptoms, and efficacy correlated with JAK inhibition in vivo and with plasma levels of compound. **Dosing** ED50 Efficacy: 16 mg/kg BID; 29 mg/kg QD ED50 JAK/STAT phosphorylation: IL-15 (JAK1/3) 3 mg/kg BID IL-6 (JAK1/2) 5 mg/kg BID; 7 mg/kg QD GM-CSF (JAK2) > 100 mg/kg BID; 91 mg/kg QD

Characterization of Inflammatory Endpoints CP-690550/10Mar10/141423	Mouse CIA Model (5 – 7 Males)	Single Dose 10 or 50 mg/kg Oral	4 hours after 50 mg/kg oral dose: Plasma cytokines IL-6, IP-10, KC, MCP-5 and MIG were significantly reduced. G-CSF and MCP-1 were not significantly reduced and there were no reductions in MIP-1α and MIP-1α levels. Acute phase proteins SAA, SAP and PTX-3 were not significantly reduced. 12 hours after 50 mg/kg oral dose: IL-6 and KC levels were no longer significantly reduced. IP-10, MCP-5 and MIG levels remained reduced. 24 hours after 50 mg/kg oral dose: All treatment-related cytokine/chemokine reductions returned to vehicle levels 4 hours after 10 mg/kg oral dose: Plasma cytokines IL-6, KC, and MCP-5 were significantly reduced.
Therapeutic Efficacy CP-690550/03Mar10/160243	Mouse CIA Model (7–8 Males)	50 mg/kg BID (Days 48-55) Oral	Statistically significant decreases in histologically assessed inflammation at 7 days and numbers of both F4/80 and CD3+ cells in tissue and joint space. No decrease in cartilage damage or inhibition of pannus formation.
Mechanism of Action CP-690550/17Mar10/165255	Mouse CIA Model (8 Males)	50 mg/kg BID (Days 48-55) Oral	Tofacitinib reduced paw severity within 3 days of treatment and showed a significant reduction by 4 days post initiation of dosing. Four hours after 50 mg/kg oral dose: G-CSF, IL-6, IP-10, MCP-1 and SAA in plasma, and G-CSF, IL-6 and MCP-1 in paw tissue were significantly reduced.
Transcriptional Profiling CP-690550/26Jan10/135046	Mouse CIA Model (10 Males)	50 mg/kg BID (Days 48-55) Oral	Statistically robust changes in STAT1 responsive genes were observed with Tofacitinib treatment at 4 hrs, as compared to vehicle treated animals. Statistically significant changes were observed in cellular markers between Days 4 and 7 of treatment; gene sets corresponding to macrophage, B-cells, T-cells and osteoclasts were repressed significantly in the tofacitinib treated group at Day 7 of treatment. Genes associated with NK cells exhibited rapid (24 hr) and robust early suppression of mRNA levels.
PK/PD Modeling CP-690550_04Nov10_150736	Mouse CIA Model (10 – 15 Males)	1.5–15 mg/kg/day SC infusion 0.5–100 mg/kg BID or QD orally (Days 22-56) Oral	**IL-15 stimulated, JAK3/JAK1- dependent STAT5 (SC infusion)** IC50 = 42 nM **GM-CSF stimulated, JAK2-dependent STAT5 (SC infusion)** IC50 = 4379 nM C_{ave} (SC pump) = 44 nM C_{ave} (BID)= 90-115 nM C_{ave} (QD) = 128-272 nM These results suggest effective inflammation modulation leading to arthritis efficacy through JAK1/3 inhibition may not require continuous coverage of the target over the day, but is more related to an optimal on and off target effect.

Evaluation Prior to Disease Development CP-690550/12Feb10/100214	Rat AIA Model (12 Females)	0.06–60 mg/kg BID or 0.06–18.5 mg/kg QD (Days 11-21) Oral	**Treatment started prior to an increase in hind paw edema** **Efficacy**: After ten days of dosing, tofacitinib reduced hind paw volume in a dose-dependent manner compared to vehicle control. ED50: <0.06 mg/kg BID 24-hr exposure AUC(0-24): < 0.23 ED50: 0.66 mg/kg QD 24-hr exposure AUC(0-24): 0.38 ug*hr/mL 6.17 mg/kg QD gave a 79% reduction in paw swelling relative to control. **Neutrophils**: After 10 days dosing tofacitinib reduced PBNC in a dose-dependent manner compared to the vehicle control. ED50: 1.7 mg/kg BID ED50: 16.7 mg/kg QD Tofacitinib did not reduce PBNC below levels measured in normal rats at doses that fully inhibited hind paw arthritis development. **Cholesterol**: After 7-10 days of dosing, tofacitinib treatment increased cholesterol in a dose-dependent manner when dosed BID and QD. ED50 ~ 1 mg/kg BID ED50 ~ 1.4 mg/kg QD. An increase in plasma IL-6, IL-17, and α2-macroglobulin was evident in AIA rats compared to normal rats by Day 18 post-adjuvant challenge. After 7-10 days of QD dosing with Tofacitinib, plasma IL-6 and IL-17 as well as α2-macroglobulin were significantly reduced >50% at doses >6.17 mg/kg QD.
Evaluation Following Disease Development CP-690550/17Feb10/102743	Rat AIA Model (12 Females)	0.02–18.5 mg/kg BID, QD or QOD (Days 14-21) Oral	**Treatment started after arthritis development** **Efficacy**: After 7 days of dosing, Tofacitinib reduced hind paw volume in a dose-dependent manner compared to the vehicle control group. ED50: ~ 0.2 mg/kg BID 24-hr exposure AUC(0-24): 1.27 ug*h/mL. ED50: 6.3 mg/kg QD 24-hr exposure AUC(0-24): 1.95 ug*h/mL. ED50: 7.1 mg/kg QOD **Neutrophils**: After 4-7 days dosing Tofacitinib reduced PBNC in a dose-dependent manner compared to the vehicle control. ED50: ~2 mg/kg BID ED50: ~11 mg/kg QD ED50: > 30 mg/kg QOD **Cholesterol**: A decrease in total plasma cholesterol was observed in AIA rats compared to normal rats by Day 14 following adjuvant injection. After 7 days of dosing, Tofacitinib treatment increased cholesterol in a dose-dependent manner when dosed BID and QD. ED50: ~0.7 mg/kg BID ED50: ~0.9 mg/kg QD ED50: 16.6 mg/kg QOD Tofacitinib treatment in AIA rats did not reduce the PBNC below normal rat levels or increase the plasma cholesterol in AIA rats above normal rat levels.
Inflammatory End Points CP-690550/10Mar10/141740	Rat AIA Model (7- 8 Females)	6.2 mg/kg QD (Days 16-22) Oral	Treatment of AIA rats with tofacitinib at the peak of inflammation resulted in rapid suppression of IL-6 and IL-17 in plasma and arthritic tissue. Suppression of these cytokines is most likely a direct effect of tofacitinib since there is no effect on paw edema at early time points. Other cytokines and á-2-macroglobulin were suppressed by tofacitinib in plasma and paw tissue after 4 and 7 days of treatment, which could be due to changes in edema and inflammatory cell infiltrates in the paw.

Therapeutic Efficacy CP-690550/03Mar10/160531	Rat AIA Model (12 Females)	6.2 mg/kg QD (Days 16-22) Oral	Statistically significant decrease in inflammation and osteoclast-mediated bone resorption 7 days after onset of therapy with 6.2 mg/kg dosing of Tofacitinib once daily and statistically significant decrease in both ED-1(CD68) and CD3-positive cells. => time-dependent decrease in inflammatory cell infiltrates and joint destruction. No effect on pannus formation or cartilage destruction.
Transcriptional Profiling CP-690550/11Dec09/112613	Rat AIA Model (7-8 Females)	6.2 mg/kg QD (Days 16-22) Oral	Statistically significant decreases in IL-6 mRNA and STAT1 responsive genes at 4 hrs as compared to vehicle treated animals. Differences did not remain significant at 24 hrs before the second dose. Gene sets corresponding to macrophage, B-cells, T-cells and osteoclasts are repressed significantly in the treated group at Day 7 of treatment. Genes associated with NK cells were significantly suppressed at Day 1 of treatment and onward.
Lipid Regulation CP-690550/16Mar10/155854	Rat AIA Model (7-8 Females)	3 or 10 mg/kg BID (Days 16-23) Oral	Peritoneal macrophages from AIA vehicle treated animals have significantly more lipid compared to naïve animals. Tofacitinib treatment (10 mg/kg QD) lowered basal lipid levels at both Day 4 and Day 7 compared to vehicle groups. There was a trend to lower lipid levels by 7 days in the 3 mg/kg group. Lipid loading of isolated peritoneal macrophages was greater in vehicle treated animals relative to naïve or tofacitinib treated rats and cholesterol present as cholesterol ester was lower in macrophages from naïve and tofacitinib treated rats.
Lipid Regulation tofacitinib_13Dec10_120754	Rat AIA Model (12 Females)	2 or 10 mg/kg BID (Days 7-18) Oral	Compared to naïve rats, AIA disease significantly reduced plasma total cholesterol and plasma cholesteryl ester (CE) and the rate of cholesterol esterification. Plasma HDL-c, apoAI, TC and PL were significantly reduced in AIA disease vs. naïve rats. Haptoglobin was increased. When measured on Day 14 post immunization, Tofacitinib dose dependently increased rat plasma cholesterol (mostly HDL-c) and apoAI relative to vehicle treated AIA rats. Tofacitinib treatment at 2 and 10 mg/kg increased plasma CE by 26% and 37%, respectively relative to vehicle treatment. Paraoxanase was increased. Tofacitinib did not affect the efflux of cholesterol from tissues to the plasma compartment. Tofacitinib treatment at 2 and 10 mg/kg dose-dependently increased the in vivo rate of cholesterol esterification by 19% and 28% to levels similar to naïve animals.
Murine delayed-type hypersensitivity Kudlacz, 2004	C57BL/6 mouse	1.87, 3.75, 7.5, 15, 30 mg/kg/d SC pump	Dose-dependent inhibition of antigen-induced footpad swelling. ED50 = 2 mg/kg associated with C_{ave} = 12 ng/mL.
Mouse transplant model : cardiac transplantation into ear pinna Kudlacz, 2004	C3H/HEN mouse	5, 10, 15, 30 mg/kg/d SC pump	Dose-dependent prolongation of graft survival in the non-vascularized model, in absence of immunosuppression.
Rat transplant model Rousvoal, 2006	Lewis Rat	SC pump	Significant prevention of development of intimal hyperplasia in aortic allografts with tofacitinib mean steady-state blood concentration of 110 ng/mL. Significant prevention of alloantibody production in aortic allograft recipients.

Effects on circulating cynomolgus monkey lymphocytes subsets Reference not mentioned	Cynomolgus monkey 10/sex	Single dose 0, 10, 50, 200 mg/kg Route not mentioned	No significant compound-related reductions in CD16+, CD3- (NK) cells for up to 2 weeks following single-day dosing. No changes in other T or B lymphocyte subsets.
Renal transplant in Cynomlogus Monkeys Borie, 2005a	Cynomolgus monkey 20 animals (Treated: n=18 Controls: n=2)	Median 12-hr blood trough levels ranging from 1 ng/mL to 147 ng/mL	Mean survival time (±SEM) in animals treated with tofacitinib (53 ± 7 days) was significantlylonger than in control animals (7±1 days) and was positively correlated with exposure to the drug. Four treated animals were euthanized at 90 days with a normal renal function and low-grade rejection at final pathology. Occurrence of rejection was significantly delayed in treated animals (46+±7 days from transplantation vs. 7±1 days in controls). Persistent anemia, polyoma virus-like nephritis (n=2), and urinary calcium carbonate accretions (n = 3) were seen in animals with high exposure. Natural killer cell and CD4 and CD8+ T-cell numbers were significantly reduced in treated animals.
Renal transplant in Cynomlogus Monkeys Borie, 2005b	Cynomolgus monkey 10 animals (MMF alone: n=2; MMF + tofacitinib: n= 8)	MMF, Combo high, Combo low Oral	Mean survival time (±SEM) in animals treated with MMF alone (23 ± 1 days) was significantly extended in animals that concurrently received tofacitinib (59.5±9.8 days). Combination animals exposed to higherlevels of tofacitinib had a significantly better survival (75.2±8.7 days) than animals that received less tofacitinib (33.3± 12.6 days). Anemia and gastrointestinal intolerance was seen in combination therapy animals.

Secondary pharmacodynamic studies

Binding studies have been conducted to assess off-target activity of tofacitinib. Moreover, a specific study was performed to investigate the impact of tofacitinib administration on circulating reticulocytes.

Table 3: Summary of secondary pharmacodynamics studies

Study type/ Study Reference	Dose (mg/kg)	Results
Effects on EPO-induced increases in reticulocytes in Cynomolgus Monkeys NP-02-005	Animals orally dosed with 5 mg/kg CP-Tofacitinib or vehicle BID for 2 days prior to a single SC injection of EPO (100 U/kg) and continuing 14 days post administration (Cmax = 382 ± 314 ng/mL; AUC(0-24) = 2980 ± 558 ng•hr/mL)	Following 2 days of CP–690,550, reticulocyte numbers dropped 33% prior to treatment with EPO whereas vehicle treated animals remained relatively constant (110%). EPO-induced increases in reticulocyte numbers were attenuated by tofacitinib treatment at 3 days post EPO (125 ± 13% Tofacitinib vs. 236 ± 41% vehicle) and 5 days post EPO treatment (192 ± 24% Tofacitinib vs.254 ± 33%). A dramatic increase in the number of reticulocytes in Tofacitinib treated animals (510% relative to Day 0 values) was observed within a week following treatment termination with resolution to baseline values by the end of the study. Although EPO as a monotherapy did not affect hemoglobin and red blood cell counts in vehicle treated animals, these parameters decreased with CP–690,550 treatment (still observed up to 2 weeks following the end of the treatment). => Hematological changes may be due to inhibition of signalling through JAK2.

Binding study 68 receptors, ion, channels, enzymes 7570532	10 µM Cloned cells, cell membranes from brain and peripheral tissues from human and rat	Significant inhibition (55%) for FLT-1 kinase (VEGFR1) with an IC50 = 3.7 µM Moderate inhibition (20 – 50%) PDE4: 44% MAO-A (rat cerebral cortex): 39% DA transporter (human recombinant): 36% BZD central (rat cerebral cortex): 32% GABA transporter (rat cerebral cortex): 28% Choline transporter (human recombinant): 26% PDE3: 21% M1 (human recombinant): 20%
Binding study 50 receptors, ion, channels, enzymes 7571347	10 µM Cloned cells, cell membranes from brain and peripheral tissues from human, rat, mouse, hamster and pig	Significant inhibition (53%) at MT3 (ML2) with an IC50 = 5.3 µM and Ki = 5.2 µM Significant inhibition (>50%) for CaMK2á (73%) with an IC50 = 12 µM for LynA Kinase (86%) with an IC50 = 2.3 µM

Safety pharmacology programme

Effects on the cardiovascular system

Table 4: Summary of Cardiovascular studies

Study reference GLP status	Species/Strain	Route	Doses	Main findings
48879-104 Not GLP	HEK293 cells stably expressing hERG channels	In vitro	10 µM	Inhibition of hERG current amplitude by 6.4%.
11GR018 (110106.QHJ) GLP	HEK293 cells stably expressing hERG channels	In vitro	0, 10, 30, 100 µM	Inhibition of hERG current of 0.8% at 10 µM, 3.6% at 30 µM and 17.8% at 100 µM. Statistical significance was achieved at 30 and 100 µM. IC50 > 100 µM (= 430-fold human unbound Cmax)
10/CG/001/00 Not GLP	Dog isolated Purkinje fibers	In vitro	0, 0.1, 1 and 10 µM	No significant effect on resting membrane potential, action potential amplitude or Vmax or APD50. Increase APD90 at 0.1 µM but no difference at 1 and 10 µM.
General pharmacology evaluation Not GLP	Isolated rat aorta	NA	1 – 100 µM	Induction of a concentration-related relaxation of KCl and norepinephrine contracted rat aorta.
General pharmacology evaluation Not GLP	Guinea pig right atria	NA	1 – 100 µM	No significant effect on basal rate of the spontaneously beating pig right atria.
General pharmacology evaluation Not GLP	Conscious rats	Oral	0, 10, 100 mg/kg	**At 100 mg/kg**: ↓ mean arterial pressure, ↑ heart rate and ↑ pO2.
11GR001 Not GLP	Conscious rats (8F/group)	Oral	0, 10, 30, 75 mg/kg For 5 days	**At ≥10 mg/kg** (ratio to human exposure: 31 based on Cmax and 13 based on AUC): Dose-dependent decreased mean, systolic and diastolic blood pressures Increase followed by a decrease in heart rate. Decreased body temperature.

745-03432 (2761) Not GLP	Telemetered conscious Cynomolgus Monkeys (4M+ PK: 3M)	Oral	0, 100, 300 mg/kg Single dose	**At ≥ 100 mg/kg** (ratio to human exposure: 27 based on Cmax and 12 based on AUC): Emesis **At 300 mg/kg** (ratio to human exposure: 30 based on Cmax and 17 based on AUC): Salivation, Transient increased heart rate (+43%) Increased blood pressure (ns). No changes in cardiac rhythm or in QT interval.

ns: Not statistically significant

Effects on the central nervous system

Table 5: Summary of CNS studies

Study reference GLP status	Species/Strain	Route	Doses	Main findings
General pharmacology evaluation Not GLP	Mouse (3M/group)	Oral	0, 3.2 to 1000 mg/kg	**At ≥ 100 mg/kg** (equivalent to 45-fold human Cmax): ↓ locomotor activity, hunched to flattened posture, splayed hind limbs, ↑ eye closure, vocalization. **At ≥ 320 mg/kg** (equivalent to 140-fold human Cmax)**:** death, seizures, twitches upon movement, ↓ respiration, pale skin, tremors, loss of righting reflex, ↓ body tone, toe pinch, tail pinch, corneal responses, exploratory behaviour, Ptosis, positional passivity, fail to climb over the inverted screen, ↓ response to provoked biting, disturbance of gait, coldness **At 1000 mg/kg:** increased intensity of the symptoms above
General pharmacology evaluation Not GLP	Mouse (4M/group)	Oral	0, 3.2, 10, 32 mg/kg	No significant effects on the incidence of twitch, myoclonus or tonic extension induced by pentyletetrazole (PTZ, 85 mg/kg) compared to control animals.

Effects on the gastrointestinal system

Table 6: Summary of gastrointestinal studies

Study reference GLP status	Species/Strain	Route	Doses	Main findings
General pharmacology evaluation Not GLP	Rat	Oral	0, 10, 30, 100 mg/kg	**At ≥30 mg/kg:** Inhibition of gastric emptying (18% at 30 mg/kg (ns) and 68% at 100 mg/kg). Reduction in geometric center which indicated a reduction in overall transport through the upper GI tract (33% at 30 mg/kg and 78% at 100 mg/kg).

Effects on the renal system

Table 7: Summary of renal studies

Study reference GLP status	Species/Strain	Route	Doses	Main findings
General pharmacology evaluation Not GLP	Rat (12 M/group)	Oral	0, 3, 10, 100 mg/kg	**At ≥ 100 mg/kg**: ↑ potassium excretion (+104%) Trend of ↓ chloride excretion (-77%) and urine volume (-32%). 6/12 animals did not urinate.

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

Pharmacokinetic and toxicokinetic studies were conducted in the rat and monkey (toxicity species), with additional studies in the mouse, rabbit and dog. The pharmacokinetics of tofacitinib were similar across species with sufficient oral exposures achieved for pharmacology and toxicology evaluation.

Methods of analysis

LC-MS/MS

Validated LC-MS/MS methods were used to determine concentrations of tofacitinib in mouse, rat, rabbit and monkey serum in the toxicity studies conducted under GLP. These methods were demonstrated to be specific for quantitation of tofacitinib over a range of 5 to 1000 ng/mL in serum.

Tofacitinib was stable in serum for 24 hours (mouse), approximately 27 hours (rat, rabbit) and approximately 22 hours (monkey) at ambient temperature; 91 days (mouse), 133 days (rat), 46 days (rabbit), and 388 days (monkey) at -20°C; and through 3 freeze/thaw cycles in all samples.

Radioactivity

[^{14}C] tofacitinib was used in metabolism and mass balance studies in mouse, rat, rabbit, monkey and human, and a tissue distribution study in rat. Radiometric methods were used to measure [^{14}C] tofacitinib -derived radioactivity in biological samples from distribution and mass balance studies. Radioactivity in plasma, urine, and bile was measured by liquid scintillation counting (LSC).

For whole body autoradioluminography (WBAL) in rat, total radioactivity in tissues was quantified by video densitometry of the digital images of the autoradiograms. [^{14}C] tofacitinib was determined using LSC in an in vitro P-glycoprotein transporter study.

Absorption

Single-dose pharmacokinetics

The single-dose pharmacokinetics of tofacitinib were investigated in rats, dogs, and monkeys following intravenous or oral administration.

Table 8: Pharmacokinetic parameters after intravenous single administration

Species (Study reference)	**Assay**	**N**	**Dose (mg/kg)**	**AUC_{0-inf} (ng.h/mL)**	**AUC_{0-t} (ng.h/mL)**	**Cl (mL/min/kg)**	**Vss (L/kg)**	**t½ (h)**
Rat DM2001-69550-015	LC-MS/MS	Study A: 4M Study B: 3M	Study A : 3 Study B: 10[a]	840	ND	62.1	2.6	0.6
Rat DM2001-69550-048	LC-MS/MS	4M	5	3200	3180	29	1.55	2.8
		4F	5	2730	2730	42.3	1.43	1.8
Dog DM2001-69550-014	LC-MS/MS	6M + 2F	3	3520	ND	19.4	1.8	1.2
Monkey DM2001-69550-014	LC-MS/MS	4M	3	2850	ND	18.2	1.7	2.1

[a] *AUC_{0-inf} values for rats receiving 10 mg/kg were normalized to 3 mg/kg*

Table 9: Pharmacokinetic parameters after oral single administration

Species (Study reference)	**Assay**	**N**	**Dose (mg/kg)**	**Cmax (ng/mL)**	**Tmax (h)**	**AUC_{0-inf} (ng.h/mL)**	**AUC_{0-t} (ng.h/mL)**	**t½ (h)**	**F (%)**
Rat DM2001-69550-015	LC-MS/MS	5M	10	261	0.5	462	ND	ND	16.5
		4M		670	0.5	1138	ND	ND	12.3
		3M	30	619	0.25	940	ND	ND	11.2
		4M	100	4390	0.9	12000	ND	ND	42.9
Rat DM2001-69550-062	LSC	3M	10	2410	0.5	4590	4330	NA	NA
		3F		3590	0.5	7900	7590	NA	NA
	LC-MS/MS	3M	10	796	0.58	1210	1130	NA	NA
		3F		2390	0.5	4690	4610	NA	NA
Rat DM2001-69550-048	LC-MS/MS	4M	10	2400	0.31	2770	2750	2.0	43.3
		4F		3670	0.25	7030	6910	1.5	129
Rabbit DM2001-69550-064	LSC	4F	30	16800	0.875	ND	69800	2.40	NA
Dog DM2001-69550-014	LC-MS/MS	2M + 2F	5	1020	0.5	2330	ND	NA	43.0
Monkey DM2001-69550-014	LC-MS/MS	2M + 1F	5	791	1.1	2280	NA	ND	48.0
Monkey DM2004-69550-052	LSC	2M	5	2820	1.5	10600	10400	8.9	NA
		2F		2730	1.5	8810	8650	6.3	NA
	LC-MS/MS	2M	5	513	1.5	1240	1240	1.4	NA
		2F		783	1.0	1820	1820	1.2	NA

ND: Not determined
NA: Not applicable

Repeat-Dose pharmacokinetics

Studies designed to specifically investigate tofacitinib exposure after multiple doses were not conducted. However, toxicokinetic studies were conducted as part of repeat-dose toxicity studies.

Rodent

In a 6-month oral gavage carcinogenicity study, CB6F1/Jic-TgrasH2@Tac mice (15/gender/group) were dosed tofacitinib as a citrate salt in 0.5% methylcellulose at 25, 75, or 200 mg/kg/day. There were no clear, apparent gender-related differences in exposure. At week 20, mean Tmax values at 25, 75 and 200 mg/kg/day were 0.5, 0.5 and 1 hour, respectively.

Toxicokinetic measurements were conducted during the 6-week, the 6-month, the 2-year carcinogenicity, two embryofetal development and photoxicity studies and in a juvenile fertility study.

Table 10: Pharmacokinetic parameters in rodents after repeated administration

Species (Study reference)	Route	Sampling time	Dose (mg/kg)	N/sex	Tmax (h)	Cmax (ng/mL)		AUC_{0-24} (ng.h/mL)	
						Total	Unbound [a]	Total	Unbound [a]
Mouse 08GR481	Oral	W20	25	3M	0.5	1380	925	1990	1333
				3F	0.5	1900	1273	1860	1246
			75	3M	0.5	3530	2365	6210	4161
				3F	0.5	4120	2760	8880	5950
			100	3M	1.0	8260	5534	20800	13936
				3F	0.5	3270	2191	13700	9179
Rat 01-2063-06	Oral	D1	1	5M	0.5	61.3	52	94.6	80
				5F	0.5	152	129	228	194
			10	5M	0.5	728	619	1690	1437
				5F	0.5	2080	1768	4100	3485
			100	5M	0.5	10400	8840	57200	48620
				5F	0.5	12600	10710	71700	60945
		D44	1	5M	0.5	109	93	136	116
				5F	0.5	236	201	322	274
			10	5M	0.5	1080	918	1850	1573
				5F	0.5	2980	2533	4730	4021
			100	5M	2	8130	6911	49400	41990
				5F	1	8860	7531	51200	43520

Species (Study reference)	Route	Sampling time	Dose (mg/kg)	N/sex	Tmax (h)	Cmax (ng/mL)		AUC_{0-24} (ng.h/mL)	
						Total	Unbound [a]	Total	Unbound [a]
Rat 02-2063-20	Oral	D1	1	3M	0.5	75.0	64	NR	NR
				3F	1	179	152	513	436
			10	3M	1	761	647	2030	1726
				3F	0.5	2460	2091	5850	4973
			100	3M	2.0	9000	7650	52300	44455
				3F	2.0	10900	9265	NR	NR
		D4	1	3M	0.5	76.1	65	NR	NR
				3F	0.5	227	193	NR	NR
			10	3M	0.5	1500	1275	3280	2788
				3F	0.5	2900	2465	6820	5797
			100	3M	2.0	9270	7880	51000	43350
				3F	1.0	9020	7667	66200	56270
		D13	1	3M	0.5	132	112	NR	NR
				3F	0.5	343	292	725	616
			10	3M	0.5	1630	1386	3550	3018
				3F	0.5	3390	2882	8000	6800
			100	3M	1.0	5630	4786	21800	18530
				3F	1.0	7640	6494	30900	26265
		D26	1	3M	0.5	120	102	NR	NR
				3F	0.5	382	325	742	631
			10	3M	0.5	1640	1394	3440	2924
				3F	0.5	3040	2584	7680	6528
			100	3M	2.0	9670	8220	43200	36720
				3F	1.0	10600	9010	68800	58480

Species (Study reference)	Route	Sampling time	Dose (mg/kg)	N/sex	Tmax (h)	Cmax (ng/mL)		AUC_{0-24} (ng.h/mL)	
						Total	Unbound [a]	Total	Unbound [a]
Rat 07GR439	Oral	W26	10	3M	0.5	1600	1360	3880	3298
				3F	0.5	2840	2414	7850	6673
			30	3M	0.5	4190	3562	12600	10710
				3F	0.5	6940	5899	30200	25670
			75	3M	2.0	7760	6596	44400	37740
			100/75[b]	3F	2.0	9450	8033	68100	57885
		D130	75	3M	1.0	5300	4505	27000[c]	22950[c]
		D129	100/75[b]	3F	1.0	6680	5678	38300[c]	32555[c]
Gravid rat 04-2063-24	Oral	GD17	1	5F	0.5	185	157	516	439
			10	5F	0.5	2690	2287	8400	7140
			30	5F	0.6	4900	4165	24000	20400
Gravid rat 09GR353	Oral	GD17	30	5F	0.6	6360	5406	29400	24990
			100	5F	1.2	9390	7982	73800	62730
			300	5F	0.5	14400	12240	108000	91800
Juvenile rat 09GR250	Oral	D1	1	3M	0.5	90.5	77	281	239
				3F	0.5	109	93	336	286
			10	3M	0.5	1320	1122	4890c	4157
				3F	0.5	1610	1369	6720	5712
			100	3M	1.0	8640	7344	69100	58735
				3F	1.0	11000	9350	71200	60520
		D35	1	4M	0.5	249	212	412	350
		D50		4F	0.5	95.3	81	148	126
		D35	10	4M	0.5	2890	2457	5620	4777
		D50		4F	0.5	1440	1224	2660c	2261
		D35	100	4M	0.5	10100	8585	77200	65620
		D50		4F	2.0	7480	6358	67500	57375
Long-Evans rat 10GR350	Oral	D7	10	5F	0.5	4270	4012	8070	6860
			30	5F	0.5	6830	5806	24900	21165
			100	5F	0.5	12000	10200	56000	47600

[a] *Unbound Cmax or AUC(0-24) = Total Cmax or AUC(0-24) x 0.67 or 0.85 (mean fraction unbound in mouse and rat plasma respectively.*
[b] *Females were dosed at 100 mg/kg/day from Day 1 to Day 132 and 75mg/kg/day from Day 133 (prior to Week 26) to terminal sacrifice.*
[c] *AUC (0-8)*
NR: Not reported

Rabbit

In an oral embryo-fetal development study, tofacitinib was administered to gravid female NZW rabbits from GD 7 to GD 19. Exposures to tofacitinib increased with increasing dose.

Table 11: Pharmacokinetic parameters in rabbits after repeated administration

Species (Study reference)	Route	Sampling time	Dose (mg/kg)	N/sex	Tmax (h)	Cmax (ng/mL)	AUC_{0-24} (ng.h/mL)
Rabbit 05-2063-25	Oral	GD 19	10	4F	0.875	610	1470
			30	4F	1.20	2490	6350
			100	4F	1.20	8220	32100

Monkey

Toxicokinetic measurements were conducted during the 4-week and the 9-monthtoxicity studies and in the 39-week juvenile study.

Table 12: Pharmacokinetic parameters in monkeys after repeated administration

Species (Study reference)	Route	Sampling time	Dose (mg/kg)	Sex	Tmax (h)	Cmax (ng/mL)		AUC_{0-24} (ng.h/mL)	
						Total	Unbound [a]	Total	Unbound [a]
Monkey 01-2063-09[b]	Oral	D1	10	F	0.7	234	152	3220	2093
			50	M+F	2.3	591	384	8930	5805
			100	F	1.5	1740	1131	28300	18395
		D29	10	M+F	2.3	194	126	2770	1801
			50	M+F	2.9	718	467	10700	6955
Monkey 2003-0301[c]	Oral	D1	0.5	M+F	0.75	21.1	14	74.1	48
			2	M+F	0.69	92.8	60	478	311
			10	M+F	0.81	439	285	2670	1736
		D107	0.5	M+F	0.56	17.8	12	64.5	42
			2	M+F	0.56	92.8	60	503	327
			10	M+F	0.69	483	314	2780	1807
		D254	0.5	M+F	0.56	19.9	13	78.6	51
			2	M+F	0.56	107	70	524	341
			10	M+F	0.57	501	326	2890	1879
Monkey 2003-0301[c]	Oral	D1	0.5	M+F	0.5	36.8	23.9	73.8	48.0
			2	M+F	0.96	116	75.4	418	272
			10	M+F	1.0	531	345	2280	1482
		W36	0.5	M+F	0.63	33.2	21.6	62.2	40.4
			2	M+F	0.61	119	77.4	424	276
			10	M+F	0.93	427	278	2360	1534

[a] Unbound Cmax or AUC(0-24) = Total Cmax or AUC(0-24) x 0.65 (mean fraction unbound in monkey plasma)
[b] TID dosing
[c] BID dosing

Distribution

Tissue Distribution

The tissue distribution of [14C] tofacitinib following a single oral gavage dose of 10 mg/kg was evaluated in male pigmented Long-Evans rats using WBAL (Study DM2004-690550-041). Distribution of radioactivity throughout the body was assessed at 0.5, 1, 2, 4, 8, 12, 24, 72, 168, and 504 hours after dosing individual animals.

[^{14}C] tofacitinib -related radioactivity distributed into at least 57 tissues evaluated in the rat. Maximum concentrations of [^{14}C] tofacitinib radioequivalents occurred at 0.5 hours for 43 tissues, at 1 hour for 10 tissues and the whole body, and at 12 hours for ocular tissues containing melanin. Drug radioequivalent concentrations were sustained in blood for at least 12 hours. Drug-related material showed limited distribution across the blood-brain barrier with a cerebral-to-systemic blood ratio of 0.05, as assessed either by Cmax or AUC; these results are consistent with tofacitinib being a substrate for P-glycoprotein. By 24 hours [^{14}C] tofacitinib radioequivalents declined below the LLOQ of 0.034 µg eq/g for 47 opyrro 57 tissues. Drug-related material was present only in intervertebral discs, liver, blood vessel walls, kidneys, and ocular tissues containing melanin at 72 hours. Only blood vessel walls and ocular tissues containing melanin still had measurable concentrations of drug-related material at 168 and 504 hours. The lens of the eye was devoid of drug-related material at all sampling times. Reversible binding to melanin is commonly seen with lipophilic amine or basic compounds and has been shown to generally have no toxicologic significance.

Plasma Protein Binding and Blood to Plasma Distribution

The fraction of tofacitinib unbound (fu) to plasma proteins in mice, rats, dogs, monkeys, and humans was determined by ultra-filtration at concentrations of 156, 1250, and 500 ng/mL (Study DM2001-609550-018). Tofacitinib showed low to moderate protein binding in all species evaluated. Collective plasma protein binding in mouse (fu 0.67), dog (fu 0.80), monkey (fu 0.65), and human (fu 0.61) was concentration independent. However, binding to rat plasma proteins decreased with drug concentration (fu 0.69 at 156 ng/mL; fu 0.91 at 1250 ng/ml; 0.94 at 2500 ng/mL). Given the species differences in plasma protein binding, safety margins based on exposure are calculated using unbound concentrations. A composite fu value of 0.85 was used to calculate unbound Cmax and AUC values in the rat toxicity studies.

Binding studies were conducted using human serum albumin and human α 1-acid glycoprotein at physiologically relevant concentrations. Tofacitinib did not appear to bind to α 1-acid glycoprotein (fu 1.16), but did appear to bind moderately to human serum albumin independent of initial concentration (fu 0.51) (Study DM2002-690550-025).

The blood-to-plasma concentration ratio for tofacitinib determined in vitro at 1 µM (312 ng/mL) was 1.2 in rat, monkey, and human, indicating relatively equal distribution of drug between the red blood cell and plasma compartments (Study CP-690550).

Metabolism

Table 13. Parent and metabolite profiling of tofacitinib in human, monkey, and rat plasma, urine, and faeces

	Human (Male)			Monkey (Male/Female)			Rat (Male/Female)		
Metabolite	Plasma (% Total Radioactivity)	Urine (% Dose)	Feces (% Dose)	Plasma (% Total Radioactivity)	Urine (% Dose)	Feces (% Dose)	Plasma (% Total Radioactivity)	Urine (% Dose)	Feces (% Dose)
Tofacitinib (Parent)	69.4	28.8	0.9	30.8/48.6	6.1/10.9	1.5/1.9	60.5/58.2	11.7/33.9	5.3/15.6
M1/M2 [a]	7.4	3.6		7.6/9.0	2.5/3.3	2.7/3.7	15.5/13.8	14.3/5.2	11.0/12.0
M2			0.5						
M4	3.9	8.2		2.5/3.9			2.4/2.6	4.1/2.7	2.4/ND
M4/M18 [a]			3.4			9.4/8.4			
M6				1.8/2.0	1.8/1.8	3.6/3.2			2.2/1.1
M6/M21 [a]								2.3/2.2	
M8		1.4			0.2/0.2				
M9	1.0	19.6	1.6	0.5/0.5	3.5/3.6	2.8/2.8	0.5/0.9		2.9/3.5
M11			1.5			1.3/1.9			
M11/M29 [a]		10.6							
M11/M20/M29[a]	6.2			35.5/21.6					
M13							1.4/ND	5.1/ND	2.8/ND
M14	3.2	3.5	1.9	2.2/2.9	1.6/2.8	2.6/2.7	1.5/1.8	3.6/3.2	5.4/1.9
M19					ND/1.1				
M20		2.2			4.0/5.6	ND/0.5			
M21							3.2/3.5		
M22			1.8			1.1/1.3			
M23				10.9/5.7	5.3/4.7				
M26				0.5/2.0	0.9/0.9				
M28				6.6/1.4	4.1/3.8				
M29					11.4/14.9		0.8/2.4	0.3/1.7	
M31		1.4			0.8/0.4	0.4/0.6			
Unknown			2.2			1.8/1.7			7.5/5.8

Data are expressed as mean percentages of tofacitinib and metabolites.
[a] *Coeluting metabolites.*

Metabolism enzymology

The in vitro metabolism of tofacitinib was evaluated in human liver microsomes in the presence of nicotinamide adenine dinucleotide phosphate (NADPH). The results indicated that tofacitinib was extensively metabolized with the formation of 5 major metabolites through demethylation (M1), oxidation of the piperidine ring side chain (M2), hydroxylated metabolite of M2 (M5), oxidation of the pyrrolopyrimidine ring (M8), and oxidation of the pyrrole moiety (M9). The role of CYP 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 CYPs and with recombinant human CYP enzymes (rCYP).

In vitro studies using human recombinant CYP isoforms indicated that tofacitinib is primarily metabolized by CYP3A4 and CYP2C19, with minimal metabolism from CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP 2C8, CYP2C9, CYP2C18, CYP2D6, CYP2E1, and CYP3A5. Additionally, incubations of tofacitinib with human liver microsomes in the presence of a potent CYP3A inhibitor, ketaconazole (1 µM) significantly (>70%)

inhibited the formation of the oxidative metabolites, while the inhibitor of CYP2D6 (quinidine, 1 µM), CYP2C9 (sulfaphenazole, 10 µM), and CYP2C19 ((+)N-3-benzylnirvanol, 10 µM) inhibited metabolism by <10%. Taken together, these data suggest that CYP3A4 plays a major role in the metabolism of tofacitinib in humans. The apparent Km and Vmax values for the combined formation of metabolites were 132.2 µM and 517.3 pmol/min/mg protein, respectively.

Clinically, poor CYP2C19 metabolizers showed approximately 15 and 17% increases in Cmax and AUC(0-∞) respectively of tofacitinib compared to extensive metabolizers confirming that CYP3A4 is the major metabolic clearance mechanism.

All metabolites of tofacitinib were less than 10% of circulating plasma parent levels, below the level where further characterization is recommended per the ICH M3(R2) guideline. While a comprehensive analysis of the activity of low level metabolites was not conducted, all metabolites of tofacitinib have or are predicted to have ⩽10% of the activity of the parent molecule for JAK1/3 inhibition based on the following rationale. Circulating metabolites, M1/M2 (together approximately 7.4% of dose) were synthesized and their JAK 1/3 50% inhibitory concentration (IC50), indicating more than 10 fold lower potency than tofacitinib. Other metabolites detected in circulation (M4, M9, and M14) were present at levels 3.9% of dose or were co-eluting metabolites (M11/M20/M29; 6.2% of dose). Predictions of potential pharmacologic activity were based on molecules with similar chemical structure from the internal discovery efforts of the applicant. For example, oxidation on the piperadine ring or on the pyrrole ring resulted in >1000 fold loss in JAK potency.

Excretion

The excretion of [^{14}C]tofacitinib was investigated in mice, rats, monkeys and human subjects.

Table 14: Mass balance studies with Tofacitinib

Species (Study reference)	Dose (mg/kg) Route	N/ sex	Sampling period (h)	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Cage wash (% dose)	Carcass (% dose)	Recovery (% dose)
Mouse 140653	31 Oral	6M	0-96h	10.1	72.1	-	4.6	0.9	**87.7**
		6F		32.1	51.2	-	4.9	0.2	**88.3**
Rat 690550-055	10 Oral	3M	0-168h	48.8	46.6	-	0.77	-	**96.2**
		3F		54.5	42.7	-	0.3	-	**97.6**
Rabbit 690500-064	30 Oral	3F	0-48h	51.5	25.0	-	-	-	**76.5**
Monkey 690500-052	5 Oral	2M	0-168h	42.6	27.2	-	17.6	-	**87.4**
		2F		55.6	28.7	-	7.5	-	**91.7**
Bile cannulated Monkey 690500-052	5 Oral	2M	0-48h	44.9	15.4	25.0	9.5	-	**95.0**
Human 690550-049	50 Oral	6M	0-192h	80.1	13.8	-	-	-	**93.9**

Excretion in Milk

The ability of tofacitinib to distribute to milk was studied in lactating female S-D rats following a single oral dose of tofacitinib at 10 mg/kg. Concentrations of tofacitinib in milk paralleled those in serum, and were approximately 2-fold higher in milk relative to serum at all time points assessed. The milk:serum $AUC_{0-\infty}$ ratio was equal to 2.08.

Pharmacokinetic drug interactions

Cytochrome P450 inhibition

The potential for tofacitinib to inhibit the 7 major human drug metabolizing CYP450 enzymes has been studied in vitro using human liver microsomes (Study DM2001-690550-020). Incubations were conducted with probe substrates for specific activities at tofacitinib concentrations of 0.3, 3.0 and 30 µM. The IC50 estimates from this study were >30 µM (9360 ng/mL) against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. Given that a clinical dose of 10 mg BID of tofacitinib results in a steady state unbound Cmax of approximately ~227 nM, these data suggest a low potential for perpetrator drug-drug interaction by tofacitinib on the metabolism of co-administered drugs that are mainly metabolized by CYP450 enzymes.

Cytochrome P450 induction

The potential for tofacitinib to induce CYP3A4 and CYP1A2 was studied *in vitro* using immortalized human hepatocytes (the Fa2N-4 cell line) and cryopreserved human hepatocytes at concentrations up to 100 µM (31,200 ng/ml). Increased CYP3A4 and CYP1A2 activity was confirmed in this in vitro model using the prototypical inducers rifampin and omeprazole (Study DM2007-04525577-001). Treatment of the Fa2N-4 cells with tofacitinib caused mild induction (1.2- to 2.5-fold) of CYP3A4 mRNA and testosterone 6α-hydroxylase activity at most concentrations tested between 0.78 and 100 µM. Treatment of the cryopreserved human hepatocytes with tofacitinib caused significant dose-dependent induction (2.5- to 6.3-fold in Lot RCP, 1.9- to 13-fold in Lot HU4026) of CYP 3A4 mRNA levels (>4-fold at ⩾25 µM of tofacitinib), but no significant induction of testosterone 6α - hydroxylase activity at the concentrations tested.

With respect to CYP1A2, tofacitinib did not show induction of mRNA levels or ethoxyresorufin-O-deethylation at the concentrations tested in Fa2N-4 cells or cryopreserved human hepatocytes.

An *in vitro* study with human cryopreserved hepatocytes assessing the inducing effect of tofacitinib on CYP2B was performed. 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.

Interaction potential related to UGTs

The *in vitro* inhibition profiles of UGT1A1, 1A4, 1A6, 1A9, and 2B7 by tofacitinib was assessed in human liver microsomes with and without 2% bovine serum albumin. In each case, the 50% inhibitory concentration (IC50) values were determined to be >100 µM, the highest concentration tested (Study CP-690550_06Jul12_110657). These inhibition values are >441 times the clinical free Cmax of approximately 227 nM at a 10 mg BID dose. In support of this in vitro profiling data, there was no clinical evidence of tofacitinib perpetrating a drug-drug interaction on ethinyl estradiol (CSR A3921071), a drug predominantly cleared by sulfation and glucuronidation (UGT1A1).

Efflux transporters

Tofacitinib was evaluated for its potential to act as a substrate for the efflux transporters P-glycoprotein and breast cancer resistance protein (BCRP) in respective Madin Darby Canine Kidney (MDCK) transfected cell lines.

Bidirectional permeability assessment of tofacitinib (3, 12, and 102 µM), determined through parental and MDR1 transfected MDCKII cell monolayers, indicated low passive permeability with high efflux ratios of approximately 20 at 3 and 12 µM. At 102 µM, the efflux ratio was approximately 10, indicating partial saturation of efflux by tofacitinib. The efflux ratio was normalized to approximately 1 in the presence of

known P-glycoprotein inhibitors verapamil (100 µM) or ketoconazole (50 µM). These data collectively indicate that tofacitinib is a substrate of P-glycoprotein.

Further, the potential P-glycoprotein inhibitory activity of tofacitinib across Caco-2 cell monolayers indicated the drug is a low potency inhibitor of digoxin transport with an estimated IC50 of 311 µM (Study PF-04524477-10/17Oct08/060532). Given a clinical dose of 10 mg BID of tofacitinib results in a steady-state unbound systemic Cmax of ~227 nM and a projected gut concentration of ~128 µM (using a gut dilution factor of 250 mL), the systemic [I]/IC50 ratio would be ~0.001 and the gut [I]/IC50 ratio would be ~0.4. Both of these ratios are significantly below the level where a digoxin interaction study would be recommended, i.e. >0.1 and >10, respectively. Tofacitinib would not be expected to increase the plasma concentrations of digoxin, or other P-glycoprotein substrates.

Tofacitinib was shown not to be a substrate for BCRP in a BCRP-transfected MDCK cell line (efflux ratio of approximately 1) using topotecan as a positive control.

2.3.4 Toxicology

Single dose toxicity

Table 15: Summary of studies

Study reference / GLP compliance	Species / Number / Sex / Group	Dose (mg/kg) / Route	Observed max non-lethal dose (mg/kg/d)	Approx. lethal dose (mg/kg)	Major findings
Study 01-2063-07 Yes	SD Rat 2/sex/group	0, 500, 1000, 2000 Oral	< 500	500	**≥ 500 mg/kg**: Death (1 animal at LD, all animals MD and HD) Salivation, stained fur, eye staining, lacrimation, partially closed eyes, nasal discharge, slow respiration, labored respiration, decreased activity, lethargy, and cold to the touch. ↓ eosinophils ↓ fibrinogen (reversible on D7) ↑ ALAT and ASAT, ↑ glucose, ↑ BUN Lymphocytolysis within the mesenteric lymph node and decreased numbers of lymphocytes within marginal zone of the splenic white pulp. **≥ 1000 mg/kg**: Distension of stomach with fluid and gas. Necrosis of individual hepatocytes. Lymphocytolysis within the splenic white pulp.
Study 09GR453 Yes	SD Rat 10/sex/dose	0, 0.5, 1, 3 IV	3	>3	No treatment-related changes or injection site findings
Study 00-2063-04 Yes	Cynomolgus Monkey 2/sex/dose	0, 13, 67, 333 3 times daily	1000	>1000	**≥ 200 mg/kg/d**: emesis and decreased activity

Repeat dose toxicity

Table 16: Summary of studies

Report No GLP compliance	Species/ Number/Sex/ group	Dose (mg/kg/day) Route	Duration	NOAEL (mg/kg/day)	Major findings
00-2063-03 No	SD Rat 5/sex/group	0, 10, 30/300/1000[a], 100 Oral	14 days	<10	**≥10 mg/kg:** ↓ WBC and lymphocytes ↓ reticulocytes Lymphoid depletion in spleen, thymus, mesenteric lymph nodes. Mild to moderate depletion of lymphoid cells **≥ 100 mg/kg:** Generalized depletion in bone marrow. **30/300/1000 mg/kg**: Death of 1 F administered 1000 mg/kg. ↓ erythroid parameters and decreased platelets. ↑ ALAT, ASAT and GGT, ↑ liver weight, Centrilobular hypertrophy ↑ Glucose, BUN, total protein, albumin and ↓ potassium considered as secondary to stress and dehydration associated with gastric enlargement. Multifocal slight to moderate necrosis of the glandular stomach.
01-2063-06 Yes	SD Rat 10 /sex/group Recovery: 5/sex (control and HD) TK: 5/sex/group	0, 1, 10, 100 Oral	6 weeks + 1 month of recovery	< 1	**≥ 1 mg/kg:** ↓ WBC, lymphocytes, eosinophils, basophils, large unstained cells (partially reversible) ↓ RBC counts, Hb, Hct (partially reversible) ↓ lymphoid cells in bone marrow (partially reversible) **≥10 mg/kg:** ↓ reticulocytes (reversible) Lymphoid depletion in spleen, thymus, mesenteric lymph nodes (reversible). **100 mg/kg:** ↑ neutrophil counts (reversible) ↑ ASAT (reversible) Small spleen and thymus.

77435 (02-2063-20) Yes	SD Rat 15/sex/group TK: 6/sex/group	0, 1, 10, 100 Oral	6 months	< 1	**≥ 1 mg/kg:** ↑ neutrophils, ↓ total WBC , absolute lymphocyte count, absolute eosinophil count, large unstained cells and/or absolute basophil count (F) ↓ RBC, Hb, Hct and/or % reticulocytes (F) Decrease in T cells CD8a+, NK cells CD161a+ and B cells CD45RA+. Liver enlargement Small lymph nodes, spleen and thymus. **≥ 10 mg/kg**: ↑ neutrophils, ↓ total WBC , absolute lymphocyte count, absolute eosinophil count, large unstained cells and/or absolute basophil count (M) ↓ RBC, Hb, Hct and/or % reticulocytes (M) ↑ glucose and ALP (F) Decreases in all lymphocytes subpopulation: T cells (CD3+), T cell subtypes (CD4+ and CD8+), B cells (CD45RA+) and NK cells (CD161+) ↓ spleen weight Atrophy of lymph nodes spleen, thymus (F) Alveolar histiocytosis and interstitial inflammation of the lungs (M) **100 mg/kg:** salivation ↓ body weight and body weight gain (M) ↑ glucose and ALP (M) ↑ globulin and ↓ TG (F) ↑ liver weight ↓ thymus weight Atrophy of lymph nodes spleen, thymus (M) and GALT Pale foci in the lungs Alveolar histiocytosis and interstitial inflammation of the lungs (6F/15 vs 0/15 in F other groups and 10M/15 vs 8/15 in controls) Liver enlargement Minimal to slight hepatocellular hypertrophy Minimal degeneration of pancreatic Langerhans islets (F)

00-2063-05 No	Cynomolgus Monkeys 1/sex/group	0, 20/500[b], 50, 200 Oral	14 days	< 50	**≥ 50 mg/kg**: emesis ↓ RBC, Hct, Hb and % reticulocytes Lymphoid depletion of thymus, spleen and mesenteric lymph node and/or depletion of the bone marrow **≥ 200 mg/kg:** Death, salivation, loose stool, hunched posture. ↑ neutrophils and ↓ lymphocytes ↑ myeloid/erythroid ratio in the bone marrow corresponding to ↓ erythroid component Dilation of the stomach and intestine, red foci in the stomach, small thymus **20/500 mg/kg**: ↓ activity, ataxia, pale skin, dehydration ↓ body weight
01-2063-09 Yes	Cynomolgus Monkeys 3/sex/group Recovery: 2/sex (control and HD)	0, 10 (3.33 TID), 50 (16.67 TID), 100 (33.33 TID)[c]	1 month + 1month of recovery	<10	**≥10 mg/kg**: loose mucoid stool with blood-like substance ↑ WBC and neutrophils , ↓ lymphocytes and RBC parameters (reversible) ↓ in T-helper lymphocytes (CD4+, CD3+), cytotoxic/suppressor T-lymphocytes (CD8+, CD3+) (reversible) ↓ in NK cells (CD16+, CD3-) (not reversible in 2 animals) Slight erythroid hyperplasia (1 animal at LD) **≥50 mg/kg**: Mortality attributed to bacterial infection secondary to immunosuppression. ↓ body weight and food consumption Loose stools, decreased activity, ↑ ALAT and ASAT (partially reversible) ↓ Ca (reversible) Lymphoid depletion of the spleen Active bacterial and viral infections secondary to immunosuppression in multiple organs. **50 mg/kg**: swollen abdomen, salivation, swelling of the jaw and neck region, nasal discharge. ↓ % and absolute reticulocytes count (reversible) Slight granulocytic depletion and decreased neutrophil storage pool **100 mg/kg**: Erythroid depletion, decrease in neutrophil storage pool and increase in immature myeloid cells Lymphoid depletion of the mesenteric lymph node

2003-0301 Yes	Cynomolgus Monkeys 4/sex/dose	0, 0.5 (0.25 BID), 2 (1 BID), 10 (5 BID)	39 weeks	< 0.5	**≥0.5 mg/kg**: ↓ lymphocytes ↓ in T helpers lymphocytes CD4+ and/or cytotoxic/suppressor lymphocytes CD8+ ↓ NK cells (CD16+) Lymphoid hyperplasia in lymphoid tissues (2M/4 at Ld, 4M/4 at MD and 3M/4+1F/4 at HD) not associated with Lymphocryptovirus. **≥ 2 mg/kg**: ↓ RBC parameters (F) **10 mg/kg**: Mortality (1F) due to erosion in the stomach associated with an infiltrative lymphoma resulting in hemorrhage into the upper GI tract. ↓ RBC parameters (M) and ↑ reticulocytes ↓ B lymphocytes CD20+ Hemorrhage in the GI tract Enlarged adrenal, kidney, spleen, mesenteric lymph nodes Mononuclear cell infiltrates in the heart. Bone marrow erythroid hyperplasia of sternum Lymphoma of B lymphocyte origin (1M+1F) associated with Lymphocryptovirus or T cell origin (1F).

Genotoxicity

Tofacitinib was tested *in vitro* in the Ames test, the chromosome aberration test, the gene mutation test, in the *in vivo/in vitro* UDS assay and in the *in vivo* rat micronucleus test.

Table 17: Summary of genotoxicity studies

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results
Ames test 01-2063-11 GLP	*S. typhi* TA 98, TA100, TA1535, TA1538 *E. coli* WP2 uvrA pKM101	10 – 5000 µg/plate +/- S9	**Negative**
Chromosome aberration test 01-2063-10 GLP	Human lymphocytes cultures	403 – 2400 µg/mL for 3 hours with metabolic activation (S9) 393 – 1200 µg/mL for 3 hours without metabolic activation 41.8 – 540 µg/mL for 24 hours without metabolic activation	**Positive** Reproducible increase in chromosomal aberration (up to 14%) observed in the 3-hour test with metabolic activation at > 1700 µg/mL in presence of cytotoxicity (≥48% mitotic suppression)
Mammalian cell mutation test 01-2063-16 GLP	HGPRT+ CHO cells	1300 – 3400 µg/mL (-S9) 600 – 110 µg/mL (+S9)	**Negative**
In vivo/in vitro UDS test 23178-0-494OECD (01-2063-17) GLP	Hepatocytes from male rats treated in vivo	0, 125, 250, 500 mg/kg Oral route Positive control group treated i.p with dimethylnitrosamide.	**Negative** At 500 mg/kg: hypoactivity, labored breathing and/or squinted eyes. No induction of unscheduled DNA synthesis at any dose level at both time points evaluated (2 to 4 hours and 14 to 16 hours).

In vivo rat micronucleus 01-2063-12 GLP	SD rats (6/sex/dose)	0, 62.5, 125, 250 mg/kg/day for 3 days Oral route Positive control group treated i.p with Mitomycin C.	**Negative** Decrease in % body weight gain in males. Treatment-related reduction in mean % PCE in males. No increase in PCE with micronuclei.

Carcinogenicity

Table 18: Summary of studies

Report No GLP compliance	Species/ Number/ group	Dose (mg/kg/day) Route	Duration	NOAEL (mg/kg/day)	Major findings
6348-463 GLP	SD rats Control and HD: 70/sex/group LD and MD: 60/sex/group	0, 10, 30, 75 (M), 100/75 (F)[a]	2 years [b] Oral	NOAEL (general toxicity) <10 NOAEL (carcinogenicity) = 10 (F) < 10 (M)	**≥10 mg/kg**: respiratory abnormalities ↓ body weight gain and food consumption (M) ↓ WBC count and absolute lymphocyte cell count Tan, white, or gray foci of discoloration in the lungs (F) Alveolar proteinosis and macrophage infiltrate in the lung (F) Angioma in mesenteric lymph node (only in LD males) Decreased cellularity of lymphocytes in lymphoid tissues **≥ 30 mg/kg**: Bacterial infections leading sometimes to death Tan, white, or gray foci of discoloration in the lungs (M) Alveolar proteinosis and macrophage infiltrate in the lung (M) Discolored and/or large testis Leydig cell adenoma Leydig cell hyperplasia Leydig cell interstitial tumor Hibernoma from brown adipose tissue(F) Cervix polyp (F **≥ 75 mg/kg** [a]: Foot sores and scabs secondary to immunosuppression Signs of immunosuppression including *C. piliform* infection leading to the death of 6 animals (F) ↓ body weight gain and food consumption (F) Thymoma (F) Pituitary adenoma (M) Spleen decreased extramedullary hematopoiesis (both sexes) and sinusoidal dilatation (F)

Table 19: Toxicokinetic results in the 2-year carcinogenicity study

Dose (mg/kg/day)	0 (Control)		10		30		75	100/75
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Number of Animals	70	70	60	60	60	60	70	70
Cmax (ng/mL)								
Day 130 (males)/129 (females)	NA	NA	NA	NA	NA	NA	5300	6680
Day 178 (males)/177 (females)	NA	NA	1600	2840	4190	6940	7760	9450
AUC(0-24) (ng•h/mL)								
Day 130 (males)/129 (females)	NA	NA	NA	NA	NA	NA	27000	38300
Day 178 (males)/177 (females)	NAd	NA	3880	7850	12600	30200	44400	68100

Table 20: Time of occurrence of some tumors

	Final Phase Sacrifice								Unscheduled sacrifice and death							
Dose	**0 (control)**		**10**		**30**		**75**	**100/75**	**0 (control)**		**10**		**30**		**75**	**100/75**
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Number examined	20	21	21	19	25	16	15	14	50	49	39	41	35	44	55	56
Hibernoma																
Body, whole cavity	0	0	0	0	0	0	0	0	1	0	0	2	1	5	2	4
Lung	0	0	0	0	0	0	0	0	0	0	0	1	0	2	1	2
Thoracic cavity	0	0	0	0	0	0	0	0	0	0	0	2	1	2	2	3
Testis																
Interstitial cell tumor	0	NA	2	NA	1	NA	7	NA	1	NA	0	NA	3	NA	7	NA
Pancreas																
Adenoma, islet cell	0	0	1	1	2	0	0	0	2	0	0	1	2	0	1	2
Carcinoma, islet cell	1	0	0	1	3	0	0	0	0	0	4	0	2	1	0	0
Thymus																
Thymoma	0	0	0	0	0	1	1	1	1	0	0	1	0	0	0	3
Body																
Angioma	0	0	2	1	1	1	1	0	0	1	3	2	2	1	1	3

Short or medium-term studies

Table 21: Summary of carcinogenicity study in transgenic mice

Report No GLP compliance	Species/ Number/ group	Dose (mg/kg/day) Route	Duration	NOAEL (mg/kg/day)	Major findings
8200-368 GLP	CB6F1/Jic-TgrasH2@Tac mouse 25/sex/group TK: 15/sex/group	0, 25, 75, 200 Positive control (MNU): 75	6 months Oral	NOAEL (general toxicity) = 25 NOAEL (carcinogenicity) ≥ 200	No oncogenic potential at any dose level. **≥ 25 mg/kg**: Mortality (1F in control, 1F at LD, 1F at MD, 1 F and 3M at HD) **≥ 75 mg/kg**: ↓ food consumption and body weight gain Femoral bone marrow focal subphyseal hypocellularity (M) Spleen cellular depletion (M) **200 mg/kg**: Hypoactivity, recumbency, Femoral bone marrow focal subphyseal hypocellularity (F) Spleen cellular depletion (F)

Other studies

Investigative carcinogenicity studies

Specific investigative studies have been conducted to investigate Leydig cell changes and hibernoma tumours findings which have been observed in the long-term carcinogenicity study.

Table 22: Summary of investigative carcinogenicity studies

Report No GLP compliance	Species/ Number/ group	Dose Route	Duration	NOAEL (mg/kg/day)	Major findings
10GR431 Not GLP	SD rat (18 F/group)	0, 10, 30, 75 mg/kg Oral	14 days	NA	Increased BAT organ weight (75 mg/kg/day) Cell proliferation (≥30 mg/kg/day) Decreased molecular targets of JAK inhibition (pSTAT5A/B, pSTAT3) (≥10 mg/kg/day) and UCP-1 protein (≥30 mg/kg/day).

11GR016 Not GLP	Leydig cells isolated from SD rats	Cells exposed to 60 or 100 ng/mL ovine PRL in presence or absence of tofacitib (0.074, 0.21, 0.76, 2.2, 10 µM)	Exposure to PRL: 20 minutes Exposure to Tofacitinib: 1 hour prior and during oPRL treatment	NA	0.076 to 10µM Tofacitinib inhibited the PRL-induced increase in STAT5 phosphorylation and in LH receptor mRNA levels in rat Leydig cells, with complete or extensive inhibition at ≥2.2 µM Tofacitinib. These results are consistent with inhibition of PRL signaling as a mechanism for induction of benign Leydig cell tumors by Tofacitinib in rats.
11GR016 Not GLP	Culture and differentiation of brown adipocytes progenitors from stromal vascular fraction of 4-day old SD rat pups	Pre-treatment with DMSO or Tofacinitib (0.001 to 3 µM) and then treatment with 250 ng/mL ovine PRL	Pre-treatment with tofacitinib: 1 hour Treatment with oPRL: 20 min	NA	In cultured rat brown adipocytes, Tofacinitib inhibits the prolactin-induced increase in phosphorylated STAT5 and basal phosphorylated STAT-3 in a concentration-dependant manner at Tofacitinib concentrations relevant to systemic exposures in the rat carcinogenicity study.

NA: Not applicable

Reproduction Toxicity

Table 23: Summary of reproductive and developmental studies

Study type / Study reference / GLP	Species; Number / sex / group	Dose (mg / kg / day) Route	Study design	NOAEL (mg / kg / day)	Major findings
FERTILITY AND EARLY EMBRYONIC DEVELOPMENT					
Fertility and embryonic development in male and female rats 05GR051 GLP	SD Rat 20/sex/dose	0, 1, 10, 100 Oral	<u>Phase 1</u> Untreated males X Treated females (14 days prior mating, throughout cohabitation period (2 weeks max) and through GD 7) <u>Phase 2</u> Untreated females X Treated males (63 days minimum beginning 28 days prior cohabitation)	NOAEL (general toxicity) =10 (M) >100 (F) NOAEL (fertility) > 100 (M) =1 (F)	*<u>Males</u>* **100 mg / kg**: Mortality (1 M) *<u>Females</u>* **≥10 mg/kg**: ↑ postimplantation loss **100 mg / kg**: ↓ pregnancy rate, ↓ number of corpora lutea, implantation sites, viable fetuses, ↑early resorptions ↑ pre-implantation loss
EMBRYO-FETAL DEVELOPMENT					
Dose-range finding study in pregnant rat 04-2063-22 Not GLP	Timed-pregnant SD rat 6/group	0, 30, 100, 300, 500 Oral	GD6 – GD17	NOAEL (maternal toxicity) < 30 NOAEL (development) < 30	*<u>Dams</u>* **≥ 30 mg/kg**: Small thymus ↓ body weight gain ↑ post-implantation loss ↓ gravid uterine weights **≥ 300 mg/kg**: Mortality (1/6 at 300 and 4/6 at 500 mg/kg) Pale skin or eyes,

					salivation, decreased activity Small spleen ↓ body weight and food consumption Complete post-implantation loss (early resorption) <u>*Fetuses*</u> **100 mg/kg**: ↓ fetal body weight Anasarca (2 fetuses) Fetal edema (1 fetus) **≥ 300 mg/kg**: No viable fetuses
Embryo-fetal development study in female rats 04-2063-24 GLP	Timed-pregnant SD rat 20/group TK: 5/group	0, 1, 10, 30 Oral	GD6 – GD17	NOAEL (maternal toxicity) ≥ 30 NOAEL (development) ≥ 30	<u>*Dams*</u> **30 mg/kg**: Small thymus (2 dams) <u>*Fetuses*</u> No treatment-related effects
Embryo-fetal development study in female rats 09GR353 GLP	Timed-pregnant SD rat 20/group TK: 5/group and 3 for control group	0, 30, 100, 300 Oral	GD6 – GD17	NOAEL (maternal toxicity) = 30 NOAEL (development) = 30	<u>*Dams*</u> **≥ 100 mg/kg:** vaginal discharge, decreased skin turgor, piloerection ↓ body weight , ↓ body weight gain, ↓ food consumption ↓ gravid uterine weight Total litter loss (7F at MD and all F at HD) ↑ number of resorptions and post-implantation loss, **300 mg/kg:** Mortality (16/25) Decreased activity, ptosis, eyes partially closed, mouth lesion, abrasion Myocardial degeneration and/or fibrosis ↓ corpora lutea <u>*Fetuses*</u> **100 mg/kg**: ↑ fetal mortality ↓ number of live fetuses, ↓ fetal body weight External malformation (Anasarca) Visceral malformation (Membranous septal defect), general anomalies (Pale heart, pale kidney) and variation (Hemorrhagic adrenal gland) Various skeletal malformations and variations

					300 mg/kg: No viable fetuses
Dose-range finding study in pregnant rabbits 04-2063-23 Not GLP	Timed-pregnant SD rabbit 6/group	0, 10, 30, 100, 300 Oral	GD7 – GD19	NOAEL (maternal toxicity) =30 NOAEL (development) =10	<u>*Dams*</u> **≥ 100 mg/kg**: Mortality (1F at 100 mg/kg and 3F at 300 mg/kg) Abortion (1F at 100 mg/kg) Early resorption ↓ gravid uterine weight **300 mg/kg**: Small thymus Stomach irritation ↓ food consumption Late resorption <u>*Fetuses*</u> **≥30 mg/kg**: ↓ fetal body weight **≥100 mg/kg**: ↓ survival rate **300 mg/kg**: No viable fetuses
Embryo-fetal development study in female rabbits 04-2063-25 GLP	Timed-pregnant NZW rabbit 20/group TK: 5/group	0, 10, 30, 100 Oral	GD7 – GD19	NOAEL (maternal toxicity) ≥ 100 NOAEL (development) = 10	<u>*Dams*</u> **≥30 mg/kg**: Postimplantation loss (early and late resorption) ↓ gravid uterine weight **100 mg/kg**: Abortion (2F) <u>*Fetuses*</u> **≥30 mg/kg**: ↓ number of viable fetuses External malformations (thoracogastroschisis, omphalocele, tail defects and cranio-facial defects) Visceral malformations (cardiovascular malformations, gallbladder absence) Skeletal malformations (fused sternebrae, vertebral/rib animalies, fused skull bones, shortened premaxilla, small eye sockets, absent caudal centra, sternoschisis) **100 mg/kg**: ↓ fetal body weight
PRE- AND POSTNATAL DEVELOPMENT					
Development and Perinatal/Postnatal Reproduction Toxicity Study in Rats LIA00468 GLP	SD Rat 25 F/group	0, 1, 10, 50 Oral	GD6 – LD20 or GD24	NOAEL (F0 general toxicity) ≥ 50 NOAEL (F0 reproduction) = 10	<u>*F0 dams*</u> **50 mg/kg**: ↓ food consumption with no consequence on body weight or body weight gain ↓ number of delivered pups Delivery of litter with all

				NOAEL (F1) = 10	pups dying between PND1 and 4 (14F/21) Termination of 16 dams because of no surviving pups <u>*F1 generation*</u> **50 mg/kg**:↓ pup viability between PND 1 and 4 and survivability between PND 4 and 21 ↓ pup weight (PND1/PND21) No effect on sexual maturation, learning ability, mating or producing viable F2 generation fetuses.

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Table 24: Summary of juvenile toxicity studies

Study type/ Study reference / GLP	Species; Number/ sex/group	Dose (mg/ kg/day) Route	Study design	NOAEL (mg/kg/ day)	Major findings
Dose-range finding in juvenile rats 09GR249 Not GLP	SD rat 10/sex/group	0, 1, 10, 100 Oral	PND 21 – 35	> 100	No treatment-related effects
Fertility study in juvenile rats 09GR250 GLP	SD rat <u>Fertility phase</u> 20/sex/group <u>TK phase</u> 14/sex/group	0, 1, 10, 100 Oral	<u>Fertility phase</u> PND 21 – 70 (M) PND 21 – 35 (F) Treated animals mated with untreated animals <u>TK phase</u> PND 21 or PND 21 – 70 (M) PND 21 -35 (F)	NOAEL (fertility) > 100	**≥10 mg/kg**: Slight dose-dependent ↓ in body weight and body weight gain (M) (PND 21 - 70) **100 mg/kg**: Transient ↓ in body weight change in the posttreatment period No effect on developmental or reproductive toxicity.
1-month juvenile rat study with a 2-month recovery 10GR307 GLP	SD rat Main study 8/sex/dose Recovery: 8/sex/dose	0, 1, 10, 100 Oral	PND 21 - 49	< 1	**≥1 mg/kg**: ↓ WBC, lymphocytes (NK cells, cytotoxic and helper T cells and B cells) and eosinophils (F) **≥10 mg/kg**: ↓ body weight gain and body weight (F) ↓ WBC, lymphocytes (NK cells, cytotoxic and helper T cells and B cells) and eosinophils (M) ↓ basophils ↓ reticulocytes ↓ thymus and spleen weights (reversible) Lymphoid organ decreased cellularity (reversible) **100 mg/kg**: ↓ body

					weight gain and body weight (M) ↓ RBC ↑ brown adipose tissue weight (reversible) All haematology effects were reversible
39-week study in juvenile cynomolgus monkeys with a 26-week recovery **(Preliminary results)** 2501-010 09GR248 GLP	Juvenile Cynolgus monkeys Main study: 4/sex/group Recovery: 3/sex/group	0, 0.5, 2, 10 Oral	Monkeys were approximately 13 months of age at the initiation of dosing	0.5	**≥ 2 mg/kg**: ↓ lymphocytes (M) ↓NK cells, effector CD8+ T cells CD8+ T-cells (M) ↓ spleen and thymus weights **10 mg/kg**: ↓ lymphocytes (F) CD4+ and CD8+ T cells, naïve CD4+ and CD8+ T cells, central and effector memory CD8+ T cells. ↓ RBC, Hb, Hct

Toxicokinetic data

Table 25: 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	0.4	1.3
			< 1 (F)	604	324	1.0	4.6
	Monkey	39 weeks	< 0.5	25.6	12.9	0.04	0.2
Carcinogenicity	Rat	2 years	< 10 (M)	3298	1360	5.3	19.1
			10 (F)	6672	2414	10.8	34
	Mouse	6 months	200	11591	3672	18.7	51.7
Reprotoxicity	Rat	Fertility	100 (M)	-	4182	-	58.9
			1 (F)	-	222	-	3.1

	Rat	Segment II	30	24990	5406	40.4	76.1
	Rabbit	Segment II	10	1470 (Total)	610 (Total)	1.4	5.2

[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 1014 ng•h/mL and Cmax of 116 ng/mL converted to unbound fraction (fu = 0.61) of 619 ng•h/mL and 71 ng/mL respective*

Local Tolerance

Table 26. Overview of the local tolerance studies

Type of Study[b]	Species/Strain	Method of Administration	Duration of Dosing	Doses[a,b] (mg/kg/day)	GLP Compliance
Local Tolerance					
Mouse Lymph node Assay	Mouse/CRA/J	In vitro	3 Days	0%, 10%, 20%, 33%	No
Primary Eye Irritation	Rabbit/New Zealand White	Ocular	1 Day	0.1 g/left eye	Yes
Primary Skin Irritation	Rabbit/New Zealand White	Dermal	1 Day	0.5 g/left flank	Yes
Ocular Toxicity and Toleration	Rabbit/Dutch Belted	Ocular	8 Days	0.01, 0.1, 1 mg/mL (BID)	No
Topical Ocular PK	Rabbit/Dutch Belted	Ocular	5 Days	0, 30, 60 µg/eye/dose BID	No
Topical Ocular Toxicity	Rabbit/Dutch Belted	Ocular	8 Weeks	0, 0.6, 6, 60 µg/eye/day	Yes
Topical Ocular Toxicity	Monkey/Cynomolgus	Ocular	2 Weeks	0, 6.6, 60 µg/eye BID	Yes
Topical Ocular Toxicity	Monkey/Cynomolgus	Ocular	8 Weeks	0.6, 6, 60 µg/eye BID	Yes
Dermal Toleration	Minipig/Gottingen	Dermal	1 Month	0.1, 0.2, 0.5, 1, 2 mg/cm^2/day	Yes
Dermal Toleration	Minipig/Gottingen	Dermal	1 Month	2.5, 5, 10 mg/cm^2/dose	Yes

BID = Twice daily;
[a] *Unless specified otherwise, all doses are expressed as mg of active moiety per kg of body weight per day.*
[b] *Unless specified otherwise, for repeat-dose toxicity studies, the NOAEL (no-observed-adverse-effect- level) is underlined.*

Other toxicity studies

Phototoxicity

Phototoxicity was evaluated as tofacitinib has significant absorbance in the UVA-UVB/visible range from 290 to 700 nm with a molar extinction coefficient (MEC) of 1004 L/Mol/cm at 320 nm.

The in vitro phototoxic potential of tofacitinib was assessed in the mouse 3T3 fibroblast neutral red uptake assay (Study 07AM087) and a 7-day pigmented rat study (Study 20008434). Tofacitinib demonstrated no phototoxic potential in the 3T3 assay at the top concentration of 1000 µg/mL and did not elicit a phototoxic response to eyes or skin in the pigmented rat study at a top dose of 100 mg/kg/day.

Blood Compatibility

No evidence of haemolysis was observed in an in vitro haemolysis compatibility study (Study 09GR482) conducted with a tofacitinib intravenous formulation in human plasma or whole blood at concentrations of 0.01 to 1 mg/mL (or with blood at 0.05 to 0.5 mg/mL).

Antigenicity

As a small molecule, antigenicity studies with tofacitinib have not been conducted.

Immunotoxicity

Studies outlined in ICH S8 do not apply since tofacitinib is intended to modulate the immune response. However, parameters that relate to immune toxicity were collected in some of the toxicology studies (haematology/immunophenotyping, lymphoid organ weights, and histology). Immunology endpoints were evaluated in basic pharmacology and general toxicology studies.

Dependence

Dependence studies with tofacitinib have not been conducted. Tofacitinib is a P-glycoprotein (PgP) substrate and has low tissue distribution to brain. CNS effects have only been observed in mice at ≥100 mg/kg and no CNS targets known to be relevant to drug dependence were identified in the CEREP panel.

Metabolites

Studies on metabolites of tofacitinib have not been conducted because no unique human metabolites were identified and no metabolites reached a percentage that would warrant further nonclinical evaluation.

Studies on impurities

A structure-based assessment with the *in sillico* tool DEREK was performed on all starting materials, intermediates, degradant, and known or anticipated impurities, including impurities CP-703,058, CP-733,315/CP-733,317, PF-05091895, PF-05087352, PF-05198213, and PF-05211077 for genetic toxicology qualification. All of the DEREK reports were provided by the Applicant allowing conclusion that there is no concern regarding the impurities CP-703,058, CP-733,315/CP-733,317, PF-05091895, PF-05087352, except for the impurities PF-05198213 and PF-05211077. Based on the submitted data, a genotoxic concern regarding impurities PF-05211077 and PF-05198213 cannot be excluded. The Applicant should qualify these impurities according to ICH Q3A.

2.3.5 Ecotoxicity / environmental risk assessment

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 = Log P = 1.15 (pH 7.3) 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				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.1	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	*Log* K_{oc} = 2.38 (0.01M CaCl2) 3.73 (Clay Loam TB-PF soil) 3.24 (Sandy soil) 4.06 (Silty loam sediment) 3.85 (Sandy sediment)			List all values
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	11000	µg/L	Species Pseudokirchinella subcapitata
Daphnia sp. Reproduction Test	OECD 211	NOEC	4800	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	2900	µg/L	Species Pimephales promelas
Activated Sludge, Respiration Inhibition Test	OECD 209	EC15 NOEC	303300 >1000	µg/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 Micro organisms: 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

Furthermore, an activated sludge inhibition test (OECD 209) has been repeated following the revised 2010 version of the protocol. A No Observed Effects Concentration (NOEC) of >1000 mg/L was reported.

Finally, tofacitinib PEC surfacewater value is above the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

2.3.6 Discussion on non-clinical aspects

Pharmacology

Tofacitinib showed selectivity for Janus kinase with IC50 of 3.2, 4.1 and 1.6 nM for JAK1, 2 and 3 respectively. The affinity for TyK2 was lower with an IC50 of 34 nM. All other tested kinases had IC50 >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, tofacitinib 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 which is a key endpoint in rheumatoid arthritis.

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 has 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.

Inhibition of JAK2 signalling pathway was demonstrated to be responsible for haematological changes (decrease of 33% in reticulocytes counts after a 2-day treatment with 5 mg/kg po corresponding to 3-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 which correspond to at least 10 times human Cmax.

With regards to safety pharmacology, 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 IC50 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 a 31-fold human Cmax and a transient increase in heart rate in monkeys at an exposure corresponding to a 30-fold human Cmax. No changes in ECG were observed.

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.

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, Cmax 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 faeces in the mouse (~60%). In the rat, the excretion was approximately equal through urine and faeces. 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.

Drug-drug interactions

In vitro, tofacitinib seems to be mainly metabolised by CYP3A4. However, in vivo, the real 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 part). The calculation of the [I]/IC50 ratio (with IC50 = 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, which allows concluding that a clinically relevant interaction with probe substrate of these CYPs is remote.

A clinically relevant interaction with CYP3A4 substrates due to tofacitinib a CYP3A4-inducing effect of tofacitinib 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. Regarding induction of CYP2B and 2C, the applicant has discussed the lack of in vitro studies on the inductive effect of tofacitinib on CYP2B and 2C. 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. The results have shown that, 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 risk of tofacitinib interaction related to UGT inhibition is 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. Actually, a clinical study performed with ketoconazole, inhibiting both CYP3A4 and P-gp, showed a ca 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 inhibit 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 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. However, since the two following conditions required to conduct in vitro uptake into a recombinant cell line expressing renal transporters, are not met: a renal clearance <50% of the total clearance and CLr >1.5*fu*GFR) (Giacomini et al, 2010), these investigations are not warranted. Of note, tofacitinib Clr is >1.5*fu*GFR but Clr<0,5Cl_T.

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.

Toxicology

Single and repeat-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.

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

The main target organ is the haematopoietic system. A partially reversible decrease in white blood cells and in particular in lymphocytes (T helper and cytotoxic, B and NK cells) was evident in rats and in monkeys. It was associated with lymphoid depletion in lymphoid organs and bone marrow. This is consistent with the pharmacological action on JAK1/3. Recovery of the decrease of NK cells (CD16+, CD3-) in the 1-month cynomolgus study was not observed in 2/4 animals at 50mg/kg/day within a one-month recovery period. Furthermore, reversibility of dose dependant effects on the white blood cells parameters was not investigated in the rat 6-month study. In the rat 6-week study at 100mg/kg/day only partial reversibility of WBC parameters, including lymphocytes, was observed at the end of the recovery period. The full clinical significance of these effects should now be addressed through clinical data.

A decrease in red blood cells parameters (decrease in RBC count, haemoglobin and haematocrit) and in reticulocytes was also observed in both species. It was associated with erythroid depletion in the bone marrow in monkeys. It is probably linked to the inhibition of JAK2/2 signalling pathway. The liver was also a target organ: an increase in hepatic enzymes (ASAT and ALAT in rats and monkeys and GGT in rats) was often accompanied in rats with increased liver weight and hepatocellular hypertrophy.

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 etiology 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 6-month rat study, degeneration of Langerhans islets and pale foci, hystiocytosis and interstitial inflammation in the lungs were also observed at the high dose of 100 mg/kg representing 60-fold human exposure based on AUC.

In the one month repeated dose toxicity study in the cynomolgus monkey at dose levels of 50 and 100 mg/kg/day active bacterial and viral infections in multiple organs (heart, kidney, gastrointestinal tract, buccal cavity, skin) were reported. These findings are secondary to 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 (Epstein-Barr (EBV)-like gamma herpes virus in cynomolgus monkeys) and one T-cell lymphoma. However, the lymphocyte hyperplasia also observed in this study was not associated with LCV. 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, cannot be explained by the Applicant. Thus, the applicant has concluded that regardless of the differences in lymphoma development between adult and juvenile monkeys, a potential risk for the development of lymphoma in adult RA patients being treated with tofacitinib is recognized. Mononuclear cell infiltrates were also observed in the heart.

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 respectively and 0.04 in monkeys based on AUC.

Genotoxicity

Tofacitinib underwent a complete genotoxicity tests battery. The Ames test was negative. However, the positive control in presence of metabolic activation was 2-anthramine on every strain, no preincubation

test was conducted, *S. typhimurium* strains TA 1537 or TA97 were not tested and no information about the batch purity was provided.

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. If it is considered that 48% is not an excessive level of cytotoxicity according to OECD and ICH guideline, the result of this test raises concern about the clastogenicity of this product. Furthermore, an increase of polyploidy was observed in absence of metabolic activation (up to 3.5%). Nevertheless, the polyploidy was observed at concentration which is 4655–fold above the Cmax (total) of the 10 mg twice daily (BID) clinical dose. Furthermore, no induction of polyploidy was observed at the next lower concentration evaluated, 116 µg/mL, which is 1000–fold above the Cmax (total) in humans at a dose of 10 mg BID. Since there is a threshold for aneuploidy induction, this effect is not considered relevant to humans. The mammalian cell mutation test was negative. The *in vivo* micronucleus test and the *in vivo* UDS assay were negative.

In summary, tofacitinib is not considered as a genotoxic component at therapeutic concentrations.

Carcinogenicity

Tofacitinib was not carcinogenic in a 6-month study in transgenic TgrasH2 mice. In a 2-year carcinogenicity in rats, it induced tumors: Leydig cell tumors and angioma in mesenteric lymph nodes in males at doses ⩾10 mg/kg and brown adipose tissue hibernomas and thymoma in females at doses ⩾30 mg/kg. Furthermore an increased incidence in islet cell carcinoma in males could raise a concern since degeneration of islets cells and increased glucose were observed in the 6-month rat study. 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 (Study 6348-463). A mechanistic demonstration of the role of inhibition of JAK on prolactin and LH regulation involved in Leydig cell proliferation can explain the Leydig cell tumors.

Regarding the aetiology of hibernomas formation, it would be related to a potential mechanism of sympathetic stimulation. This hypothesis is supported by decreased blood pressure and reflex increases in heart rate observed in rats. In RITA database, no hibernomas were observed compared to Covance database in which the individual group incidences ranged up to 4.6% for malignant hibernomas and 3.3% for benign hibernomas. However, there is an increase in spontaneous background incidence of hibernomas (benign and/or malignant) in rats from Covance carcinogenicity studies carried out from 2007 to 2010. This observation is also reported in published literature. Moreover, the most recent available studies in the RITA database were initiated in 2004 and 2006. In contrast, all of the studies in the Covance database were initiated in 2007 or later. Therefore, even if hibernomas are considered as rare tumors in rats, the Covance database revealed an increase background incidence of this type of tumor since 2007. Based on Covance historical data, the dose of 10 mg/kg can be considered as a NOEL for hibernomas in females.

Concerning the incidence of thymomas, the incidence of benign thymomas in females treated at 100/75 mg/kg/day (females were dosed at 100 mg/kg/day to day 132 reduced to 75 mg/kg/day in week 19 due to mortality from bacterial infection) which represents 6.3%, exceeds the range of the incidence of this type of tumor in Covance database and RITA database either (4.7% and 6.1% respectively). Consequently, the original conclusions in the study report of the 2-year rat carcinogenicity study of tofacitinib (Study 6348-463) are not changed regarding the increased incidence of benign thymomas only at the high dose in female rats. However, it should be noted that the increased incidence of thymomas in females at the top dose (75/100 mg/kg/d.) is 187–fold above the unbound AUC at the clinical dose of 5 mg BID. In addition, at 30 mg/kg, the incidence of thymomas was not increased in female at an exposure representing is 94-fold the unbound AUC at the clinical dose of 5 mg BID. The calculation of these exposure ratios was not detailed. However, based on the exposure ratio at 10 mg BID, it can be considered that the tumors occur at a very high level of exposure compared to human exposure.

Finally, the incidence of the pancreatic islet tumors observed in the 2-year rat carcinogenicity study of tofacitinib (Study 6348-463) falls within the range of the incidence of this type of tumors reported in Covance and RITA databases.

Reproductive toxicity

Tofacitinib had no effect on male rat fertility, but decreased female fertility, as evidenced by a decrease in pregnancy rate and viable foetuses and an increase in pre- and postimplantation in females with a safety margin of 3.

Tofacitinib was teratogenic in rats and rabbits. It induced a wide range of external, visceral and skeletal malformations in presence of maternotoxicity in rats but in absence of maternotoxicity in rabbits with a safety margin of 40 and 2 in rats and rabbits respectively with the therapeutic dose of 10 mg BID. Tofacitinib induced a decrease in F1 pups survival in absence of maternal toxicity. No effect on F1 generation sexual maturation, learning ability or mating was observed.

Juvenile toxicity studies

Administration of tofacitinib to juvenile animals did not impair male or female fertility in rats and resulted in the same toxicity (immune and hematologic toxicity) as in adult animals at approximately the systemic same exposure level.

Other studies

The sensitization, eye irritation and skin irritation potential of tofacitinib were evaluated. These studies are of limited relevance because tofacitinib is intended to be administered by oral route.

Tofacitinib did not induce haemolysis in human whole blood. It did not show phototoxicity potential *in vitro* or *in vivo*.

Impurities

Different batches of tofacitinib were tested in toxicity studies. The Applicant has provided DEREK reports for each impurity. In addition, a short analysis of the DEREK reports of the impurities PF-05198213 and PF-05211077 was also provided. Impurities PF 05198213 and PF-05211077 were not present in the batches used in the genotoxicity studies but were present in the batch used in the 39-week juvenile monkey study. Impurity PF 05198213 specified at 0.3% was found to contain a DEREK genotoxicity alert in the internal DEREK software. This alert is related to the nitrile function seen in the structure of the impurity PF 05198213. Moreover, the rationale based on the steric hindrance of PF-05198213 involving a local decrease in electrophilicity, is not supported. The CHMP noted that a possible intramolecular 6-membered ring like structure is possible. Delocalisation of the electronic doublet hold by the nitrogen atom is less susceptible to delocalize and therefore cannot be compared with PNU-0014508 structure. Thus the negative result in a screening Ames assay for PNU-0014508 cannot be sufficient to consider that PF-05198213 is not mutagenic. Consequently, the absence of DEREK genotoxicity alert on this impurity is not endorsed by the CHMP and this impurity should be qualified regarding the genotoxic concern. The impurity PF-05211077 does not contain any DEREK genotoxicity alert. Nevertheless, the specification is $\leqslant$0.3%, i.e. above the qualification threshold defined by ICH Q3A. Therefore, this impurity should be qualified regarding genotoxicity. In conclusion, the CHMP requested the applicant to perform an Ames test on impurities PF-05198213 and PF-05211077 according to ICH Q3A and to provide a timetable for the conduct and reporting of these studies.

2.3.7 Conclusion on the non-clinical aspects

Then non-clinical data have shown that tofacitinib is a potent inhibitor of T-cell proliferation and differentiation. The cynomolgus monkey studies have shown a decrease in NK cells and a 50% decrease in CD8+/C4+ cells. The NK cell decrease was irreversible in some animals. Some animals also developed EBV-driven lymphomas due to immunosuppression. Studies following chronic dosing with tofacitinib have shown a selective effect CD8+ effector memory cells, a selective suppression of T-cell proliferation and differentiation and an effect on the immune system (particularly on T-cell proliferation and differentiation) with a narrow therapeutic index.

The non-clinical data also raise concerns about certain effects of tofacitinib that need to be explored further as part of the safety profile in humans. The effects on the hematopoietic system, the gastrointestinal tract, the heart, the lung and the potential carcinogenic effect seem to be relevant in humans based on the safety review of clinical trials.

The CHMP also requested the applicant to perform an Ames test on impurities PF-05198213 and PF-05211077 according to ICH Q3A and to provide a timetable for the conduct and reporting of these studies.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development program of tofacitinib consisted of 21 completed Phase 1 studies, 8 Phase 2 studies (6 completed, 2 ongoing), 6 Phase 3 studies (4 completed, 2 ongoing), and 2 ongoing, open-label, extension studies.

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.

A request for a routine and triggered GCP inspection (INS/GCP/2011/027) was adopted by the CHMP for the following clinical studies:

- A3921045 (phase 3, randomized, double blind, placebo-controlled study of 2 doses of tofacitinib in monotherapy in patients with active rheumatoid arthritis).

- A3921044 (phase 3 randomized, double blind, placebo controlled study of 2 doses of tofacitinib in patients with active rheumatoid arthritis on background methotrexate (1-year analysis)

The inspections took place at three investigators' sites and at the sponsor site.

Based on the GCP inspection findings, the CHMP concluded that, overall, the data quality appeared to be a good compliance with GCP and raw data appear to be reliable for both 1044 and 1045 trials. However, the major and critical findings suggested some deficiencies in the presentation of data in the CSRs yielding the inspectors to request additional reanalysis. These analyses were generally endorsed by the inspectors and it has been concluded that there was no impact on the results. Therefore, the clinical data was considered reliable by the CHMP, as the re-analysis of all primary endpoints (including the radiological endpoint) with the FAS had no impact on the results.

- Tabular overview of clinical studies

Table 27. Overview of Clinical Studies

Study	Study Design / Length	Treatment Groups	N
Phase 3			
Background DMARD Studies*			
A3921032	MC, DB, PG, PC, R, Background MTX 6 Months	tofacitinib: 5 mg BID 10 mg BID Placebo → tofacitinib 5 mg BID at 3 months Placebo → tofacitinib 10 mg BID at 3 months	 133 134 66 66
A3921044	MC, DB, PG, PC, R, Background MTX 24 Months	tofacitinib: 5 mg BID 10 mg BID Placebo → 5 mg Placebo →10 mg NR advance to next period at 3 months, All advance to next period at 6 months	 321 319 81 79
A3921046	MC, DB, PG, PC, R, Background DMARD 12 Months	tofacitinib: 5 mg BID 10 mg BID Placebo → 5 mg Placebo → 10 mg NR advance to next period at 3 months, All advance to next period at 6 months	 318 318 79 80
A3921064	MC, DB, PG, PC, R, Background MTX 12 Months	tofacitinib: 5 mg BID 10 mg BID Placebo → 5 mg Placebo → 10 mg Adalimumab 40 mg sc QOW NR advance to next period at 3 months, All advance to next period at 6 months..	 204 201 56 52 204
Monotherapy Studies			
A3921045	MC, DB, PG, PC, R 6 Months	tofacitinib 5 mg BID 10 mg BID Placebo →5 mg tofacitinib at 3 months, Placebo → 10 mg BID tofacitinib at 3 months	 244 245 61 61
Phase 2			
Background DMARD Studies*			
A3921025	MC, DB, PG, PC, R, Background MTX 6 Months	tofacitinib: 1 mg BID 3 mg BID 5 mg BID 10 mg BID 15 mg BID 20 mg QD Placebo NR on Placebo, tofacitinib 1 and 3 mg BID and 20 mg QD → 5 mg BID at 3 months.	 71 68 71 75 75 80 69

Table 27. Overview of Clinical Studies

A3921039	MC (in Japan), DB, PG, PC, R, Background MTX 3 Months	tofacitinib : 1 mg BID 3 mg BID 5 mg BID 10 mg BID Placebo	28 28 28 28 28
Monotherapy Studies			
A3921035	MC, DB, PG, PC, R 6 Months	tofacitinib: 1 mg BID 3 mg BID 5 mg BID 10 mg BID 15 mg BID Adalimumab 40 mg sc QOW for 10 weeks →5 mg BID at 3 months Placebo NR on Placebo, tofacitinib 1 and 3 mg BID →5 mg BID at 3 months.	54 52 50 61 57 53 59
A3921040	MC (in Japan), DB, PG, PC, R 3 Months	tofacitinib: 1 mg BID 3 mg BID 5 mg BID 10 mg BID 15 mg BID Placebo	53 53 52 53 54 53
Supportive Studies			
A3921024	LT, OL	tofacitinib 5 mg BID tofacitinib 10 mg BID	2823[†]
A3921041	LT, OL (in Japan)	tofacitinib 5 mg BID tofacitinib 10 mg BID	404[†]
A3921019	R, DB, PC, MC 6 weeks	tofacitinib: 5 mg BID 15 mg BID 30 mg BID Placebo	61 69 69 65

2.4.2. Pharmacokinetics

The clinical pharmacology is derived from 13 in vitro studies, 21 Phase 1 studies comprising 17 clinical pharmacology and 4 bio pharmaceutics studies, 5 Phase 2 studies and 1 Phase 3 study providing population PK information and 5 Phase 2 studies and 2 long term extension studies providing exposure-response information.

Absorption

Oral absorption of tofacitinib, whether administered as single or multiple doses, is rapid and independent of dose. Tofacitinib is classified as a Biopharmaceutics Classification System (BCS) Class III compound (i.e. high solubility, low permeability). The human oral bioavailability study (A3921077) showed that the mean absolute oral bioavailability of the commercial tablet was 74%. The two food effect studies (A3921076 and A3921005) showed an influence on Cmax only, with a significant decrease in tofacitinib mean Cmax of 26-32%. There is no significant impact on AUC.

Bioequivalence:

Study A3921075 established bioequivalence between the Phase 2B, Phase 3 and the commercial tablet formulations. The 5 mg (lowest strength) commercial tablet uses the same blend as the 10 mg commercial tablet and shares the same manufacturing process. Both the 5 mg and the 10 mg tablets dissolve rapidly (>80% in 15 minutes using basket at 100 rpm in 0.1N HCl). Thus, the 5 and 10 mg strength commercial tablets are also considered to be bioequivalent.

Distribution

Following IV dosing, the apparent steady-state volume of distribution (Vss) of tofacitinib was estimated to be 87 L, suggesting distribution into tissues. The fraction of tofacitinib unbound (fu) to plasma proteins in humans was determined by in vitro methods to be 0.61. This low to moderate protein binding suggests low potential for drug interactions due to drug displacement. Tofacitinib does not bind to α1-acid glycoprotein (fu ~1), but binds moderately to human serum albumin (fu 0.51).

Elimination

The metabolism of tofacitinib is primarily mediated by CYP3A4.

The mass balance 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). When the apparent oral clearance (CL/F) of tofacitinib was compared between RA patients and healthy volunteers, it was found that a typical RA patient has a 43% lower CL/F (~20 L/h) compared to a healthy adult (~35 L/h). The Applicant postulated that the difference may be attributed to down-regulation of cytochrome P450s.

The Applicant provided data to support extrapolation of dosing recommendations from studies conducted in subjects/volunteers without RA to RA patients.

Inter-conversion

Tofacitinib has 2 chiral centres at C3 and C4, as indicated in the structure provided, giving 4 possible stereoisomers. The absolute configuration at the 3-position is the R configuration. The absolute configuration at the 4-position is the R configuration. No data regarding stereo-conversion of the R-R isomer is provided. All the analytical techniques used in the clinical PK program are achiral.

Dose proportionality and time dependencies

Cmax is approximately dose proportional at least up to 5 times the highest therapeutic dose of 10 mg. The conclusion of dose-proportionality is accepted by the CHMP as supported by the Phase 1 studies as well as the population PK analysis of data from five phase 2 studies. There is no evidence of time-dependency.

Pharmacokinetics in target population

Pharmacokinetic in target population was based on a population PK analysis of 5 Phase 2 studies, with supportive information from a DDI study with methotrexate (A3921013) and a Phase 3 study (A3921064). The methodology employed by the Applicant is endorsed, including the approach to model building and covariate modelling and assessment of goodness of fit and predictive performance.

Table 28 Parameter Estimates from Population Pharmacokinetic Model

	Point Estimate	% RSE	90% CI	IIV	IOV
CL/F	18.4 (L/h)	8.48	16.1, 22.7	26.6 (CV%)	
V/F	96.0 (L)	1.76	92.8, 99.6	26.0 (CV%)	
D1	0.352 (h)	12.0	0.267, 0.410		
F1	1	Fixed			23.0 (CV%)
Inter-individual Variance					
$\Omega^2_{CL/F}$	0.0707	16.0	0.0558, 0.0931		
$\Omega^2_{CL/F - V/F}$	0.0112	86.3	0.00052, 0.0314		
$\Omega^2_{V/F}$	0.0674	13.7	0.0518, 0.0807		
Inter-occasionVariance					
Ω^2_{F1}	0.0528	20.8	0.0371, 0.0878		
Residual variance					
σ^2_{prop}	0.118	6.57	0.106, 0.132		
$\sigma^2_{prop, trough}$	0.411	29.7	0.166, 0.527		
Prop. Error CV	34.4 (CV%)				
Prop. Error CV(trough)	64.1 (CV%)				

%RSE: relative standard error; CI: confidence interval; IIV: inter-individual variance; IOV: inter-occasion variance; CV: coefficient of variation; CL/F: apparent oral clearance; V/F: apparent volume of distribution; D1: zero-order absorption duration; F1: relative bioavailability. Source: PMAR-00178

Table 29 Covariate Parameter Estimates from the CP-690,550 Population Pharmacokinetic Model in RA Patients

Parameter	Covariate	Estimate	%RSE	90%CI
CL/F	Weight	0.0427	292	-0.215, 0.268
CL/F	Age	-0.0629	135	-0.253, 0.0896
CL/F	Sex	1.08	8.79	0.873, 1.23
CL/F	Black	1.05	10.9	0.806, 1.28
CL/F	Asian	1.00	8.32	0.814, 1.20
CL/F	Hispanic	1.02	5.87	0.871, 1.12
CL/F	Other Race	0.781	10.2	0.620, 0.925
CL/F	CLcr	0.364	36.3	0.202, 0.684
CL/F	Study 1025	1.17	5.17	1.03, 1.29
V/F	Weight	0.882	7.47	0.757, 0.979
V/F	Age	-0.319	19.4	-0.409, -0.177

%RSE: relative standard error ; CI: confidence interval; CL/F: apparent oral clearance; V/F: apparent volume of distribution; CLcr: creatinine clearance
Source: PMAR-00178

The Applicant has also provided data from subpopulations of special interests (e.g. patients with reduced renal function, patients undergoing dialysis and African-American population and has proposed to update the SmPC accordingly.

Special populations

The PK studies in hepatic and renally impaired subjects were conducted in subjects with mild/moderate/severe renal impairment or mild/moderate hepatic impairment.

Pharmacokinetic interaction studies

In-vitro studies suggest that the metabolism of tofacitinib is mediated by CPY3A4 and CYP2C19. The compound is a substrate for P-gp. The potential to inhibit transporters such as P-glycoprotein, organic anion transporting polypeptide 1B1 or 1B3 or organic cation transporter are low.

The applicant has conducted 7 in vivo studies assessing the potential for drug interactions in humans summarised below: methotrexate (MTX) (A3921013), fluconazole (A3921014), tacrolimus (Tac) andmcyclosporine (CsA) (A3921020), ketoconazole (A3921054) and rifampin (A3921056). The effect of tofacitinib on the PK of other drugs was evaluated in the following studies: midazolam (A3921059), oral contraceptives (A3921071) and MTX (A3921013).

Study A3921013

Study A3921013 (15/04/2005-05/06/2006) was an open-label, non-randomized, fixed sequence, DDI study in subjects with rheumatoid arthritis (RA) receiving a stable, weekly oral dose of methotrexate (MTX) to estimate the effect of tofacitinib on MTX PK and the effect of MTX on tofacitinib PK. Subjects

received their weekly- individualized MTX dose on the morning of Day 1. Subjects received 30 mg tofacitinib every 12 hours from Days 3 to 6. On Day 7, subjects were co-administered their weekly individualized MTX dose along with 30 mg tofacitinib. Twelve (12) males and females, aged 36-73 years inclusive, completed the study.

The 90% CIs for the adjusted mean ratios of tofacitinib AUC(0-tau) and Cmax (with and without MTX) were contained entirely within the 80.00%-125.00% intervals. No major changes in Tmax or t1/2 were observed. Upon co-administration with tofacitinib, mean MTX AUC(0-tau) and Cmax decreased by 10% and 13% , respectively. No major changes in MTX Tmax or t1/2 were observed.

Study A3921014

Study A3921014 (19/11/2005-23/12/2005) was an open-label, single fixed-sequence, DDI study in healthy subjects to estimate the effect of fluconazole on tofacitinib PK. Subjects received a single dose of 30 mg tofacitinib on Day 1 of Period 1. On Day 1, Period 2, the subjects were administered fluconazole 400 mg followed by 200 mg QD on Days 2-7. On Day 5, subjects were administered a single 30 mg oral dose of tofacitinib while being administered the dose of fluconazole 200 mg QD. Twelve (12) males, aged 23-49 years inclusive, completed the study.

Table 30 **Descriptive Statistics and Statistical Comparisons Following a Single Oral Dose of 30 mg CP-690,550 Alone and in Combination with Fluconazole (A3921014)**

Parameter (Units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
	CP-690,550 + Fluconazole (Test)	CP-690,550 Alone (Reference)		
Cmax (ng/mL)	351	277	126.74	111.82, 143.66
AUC(0-∞) (ng·h/mL)	1770	987	179.26	163.81, 196.16
Tmax (h)[b]	0.8 (0.3-1.0)	0.5 (0.5-2.0)		
t1/2 (h)[c]	4.00 (0.70)	2.97 (0.59)		

CI=Confidence interval; MTX = Methotrexate
[a] The ratios (and 90% CIs) are expressed as percentages.
[b] Median (Range) are reported for Tmax
[c] Arithmetic mean (SD) are reported for t1/2
Source: CSR A3921014, Tables 13.5.2.4, 13.5.2.5, Table 13.5.3

Co administration of tofacitinib with multiple dose fluconazole resulted in 79% and 27% mean increases in AUC(0-∞) and Cmax, respectively. Tmax values were comparable between the two treatment periods while t1/2 increased in the presence of fluconazole.

Study A3921020

Study A3921020 (29/06/2009-05/08/2009) was an open-label, single fixed-sequence, DDI study to estimate the effects of Tacrolimus (Tac) and Cylcosporine (CsA) on tofacitinib PK. Subjects were randomized to 1 of 2 cohorts (Cohort A: Tac; Cohort B: CsA). In each cohort, subjects received a single dose of 10 mg on the morning of Day 1 of Period 1. In Period 2, subjects received either Tac q12h on Days 1 through 7 (Cohort A) or CsA q12h on Days 1 through 5 (Cohort B). Subjects received the last dose of Tac or CsA simultaneously with a single oral dose of 10 mg tofacitinib on Days 8 and 6, respectively. The planned doses of Tac and CsA were 5 mg q12h and 200 mg q12h, respectively, and were adjusted to achieve therapeutic concentrations based on predose levels on Day 3. Twenty-two (22) males ranging in age from 22 to 49 years completed the study.

Table 31 Descriptive Statistics and Statistical Comparisons Following Single 10 mg Oral Doses of CP-690,550 Alone and in Combination with Tacrolimus and Cyclosporine (A3921020)

Parameter (Units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
Tacrolimus				
	CP-690,550 10 mg with Multiple Dose Tac (Test)	CP-690,550 10 mg Alone (Reference)		
Cmax (ng/mL)	94.7	104	90.76	83.17, 99.03
AUC(0-∞) (ng·h/mL)	411	339	121.12	113.24, 129.55
Tmax (h)[b]	1.0 (0.5-2.0)	0.5 (0.5-1.0)		
t1/2 (h)[c]	3.77 (0.49)	3.39 (0.29)		
Cyclosporine				
	CP-690,550 10 mg with Multiple Dose CsA (Test)	CP-690,550 10 mg Alone (Reference)		
Cmax (ng/mL)	93.1	112	83.19	71.37, 96.96
AUC(0-∞) (ng·h/mL)	533	308	173.13	161.79, 185.26
Tmax (h)[b]	1.0 (0.5-2.0)	0.5 (0.5-1.0)		
t1/2 (h)[c]	3.91 (0.32)	3.21 (0.32)		

Tac = Tacrolimus; CsA = Cyclosporine; CI= Confidence interval
[a] The ratios (and 90% CIs) are expressed as percentages.
[b] Median (Range) are reported for Tmax
[c] Arithmetic mean (SD) are reported for t1/2
Source: CSR A3921020, Table 13.5.2.1, Table 13.5.3.1, Table 13.5.3.2

Coadministration of tofacitinib with multiple dose Tac resulted in 9% mean decrease in Cmax and a 21% mean increase in AUC(0-∞) of tofacitinib. Coadministration of tofacitinib with multiple dose CsA resulted in 17% mean decrease in Cmax and a 73% mean increase in AUC(0-∞) of tofacitinib. Median Tmax was 0.5 hours (range: 0.5 to 1.0 hours) for tofacitinib alone and 1.0 hours (range: 0.5 to 2.0 hours) with Tac or CsA. No major changes in t1/2 were observed with either of the combination treatments, compared to tofacitinib alone.

Study A3921054

Study A3921054 (06/09/2010-25/09/2010) was an open label, single fixed sequence, DDI study to estimate the effect of ketoconazole on tofacitinib PK. Subjects received a single dose of 10 mg tofacitinib on Day 1 of Period 1, which was followed by administration of ketoconazole 400 mg q24h on Days 1 to 3 of Period 2. On Day 3, subjects simultaneously received a single dose of 10 mg tofacitinib while being on 400 mg ketoconazole q24h. Twelve (12) males, aged 22-53 years inclusive, completed the study.

Table 32 Descriptive Statistics and Statistical Comparisons Following Single 10 mg Oral Doses of CP-690,550 Alone and in Combination with Ketoconazole (A3921054)

Parameter (Units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
	CP-690,550 10 mg + Ketoconazole 400 mg (Test)	CP-690,550 10 mg (Reference)		
Cmax (ng/mL)	91.6	78.8	116.24	104.59, 129.18
AUC(0-∞) (ng·h/mL)	488	240	203.23	190.96, 216.30
Tmax (h)[b]	1.0 (0.5-2.0)	0.5 (0.5-1.0)		
t1/2 (h)[c]	3.91 (0.53)	2.85 (0.37)		

CI= Confidence interval
[a] The ratios (and 90% CIs) are expressed as percentages.
[b] Median (Range) are reported for Tmax
[c] Arithmetic mean (SD) are reported for t1/2
Source: CSR A3921054, Table 14.4.3.1, Table 14.4.3.3

Coadministration of tofacitinib with multiple dose ketoconazole resulted in approximately 103% and 16% mean increases in AUC(0-∞) and Cmax, respectively. Mean terminal t1/2 increased from 2.9 hours for tofacitinib alone to 3.9 hours for tofacitinib with ketoconazole. Median Tmax increased from 0.5 h for tofacitinib alone to 1.0 h with ketoconazole.

Study A3921056

Study A3921056 (10/08/2010-11/10/2010) was an open label, single fixed sequence, DDI study to estimate the effect of rifampin on tofacitinib PK. Subjects received a single dose of 30 mg tofacitinib on Day 1 of Period 1, which was followed by administration of rifampin 600 mg q24h on Days 1 to 7 of Period 2. On Day 8 of Period 2, subjects received a single dose of 30 mg tofacitinib. Twelve (12) males, aged 23-50 years inclusive, completed the study.

Table 33 Descriptive Statistics and Statistical Comparisons Following Single 30 mg Oral Doses of CP 690,550 Alone or After 7 Days of Rifampin (A3921056)

Parameter (Units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Geometric Means[a]	90% CI for Ratio
	CP-690,550 30 mg SD After 7 days of Rifampin 600 mg q24h (Test)	CP-690,550 30 mg SD Alone (Reference)		
Cmax (ng/mL)	65.7	250	26.32	22.63, 30.61
AUC(0-∞) (ng·h/mL)	137	848	16.10	14.24, 18.20
Tmax (h)[b]	0.5 (0.5-2.0)	0.5 (0.5-1.0)		
t1/2 (h)[c]	2.86 (1.58)	4.19 (0.68)		

CI= Confidence interval; q24h = Every 24 hours; SD = Single dose
[a] The ratios (and 90% CIs) are expressed as percentages.
[b] Median (Range) are reported for Tmax
[c] Arithmetic mean (SD) are reported for t1/2
Source: CSR A3921056, Table 14.4.3.1, Table 14.4.3.3

Administration of 600 mg q24h rifampin for 7 days followed by a 30 mg single dose of tofacitinib resulted in approximately 84% and 74% mean reductions in AUC(0-∞) and Cmax, respectively. Mean t1/2 for tofacitinib decreased from 4.2 hours to 2.9 hours in the presence of rifampin. No change in median Tmax was observed following rifampin administration.

Study A3921059

Study A3921059 (11/06/2009-31/07/2009) was an open-label, randomized, 2-period crossover DDI study to demonstrate the lack of an inhibitive or inductive effect of tofacitinib on midazolam PK. In Sequence 1, subjects received a single dose of midazolam 2 mg oral (PO) syrup followed by multiple BID dosing of 30 mg tofacitinib for 6 days and concurrent single dose of midazolam 2 mg PO syrup on Day 7. In Sequence 2, subjects were dosed with tofacitinib 30 mg PO BID for 7 days with a concurrent single dose of midazolam 2 mg PO syrup on Day 7. Subjects then underwent a washout period of at least 7 days and received a single dose of midazolam 2 mg PO syrup. Twenty-four (24) males, aged 22-55 years inclusive, completed the study.

The 90% CIs for the ratios of adjusted geometric means for AUC(0-∞) and Cmax were entirely contained within the acceptance range (80.00%, 125.00%), indicating that tofacitinib had no net inhibitive or inductive effect on the PK of midazolam. Mean t1/2 and Tmax were similar for both treatments.

Study A3921071

Study A3921071 (07/06/2010-29/07/2010) was an open-label, randomized, 2-period crossover DDI study to demonstrate the lack of an inhibitive or inductive effect of tofacitinib on the PK of the oral contraceptives (OCs), ethinyl estradiol and levonorgestrel. In Sequence 1, subjects received a single dose

of OCs in the form of 1 Microgynon 30® tablet followed by multiple BID dosing of 30 mg tofacitinib for 10 days and a concurrent single dose of OCs on Day 11. In Sequence 2, subjects were dosed with tofacitinib 30 mg PO BID for 11 days with a concurrent single dose of OC on Day 10. Subjects then underwent a washout period of at least 10 days and received a single dose of OCs. Nineteen (19) females, 19-50 years of age inclusive, completed the study.

The 90% CIs for the ratios of adjusted geometric means for AUC(0-∞) and Cmax were entirely contained within the acceptance range (80.00%, 125.00%), indicating that tofacitinib had no net inhibitive or inductive effect on the PK of ethinyl estradiol or levonorgestrel. For both agents, t1/2 and Tmax values were similar with and without coadministration of tofacitinib.

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), cyclosporine and ketoconazole; Increases in Cmax following administration with fluconazole and ketoconazole; Decreases in Cmax and AUC following administration with rifampicin.

Exposure-safety relationships

White blood cells: Phase II data illustrated a significant dose-related reduction in NK cells with 36% decrease for the 5 mg dose and 47% decrease for the 10 mg dose at 24 weeks. Neutrophil counts showed a nadir at 6-8 weeks with the 10 mg dose showing an incidence of x1.4 (mild neutropaenia) and x1.6 (moderate neutropaenia) compared to the 5 mg dose.

Serious infections: Exposure-response analysis of data from patients who participated in the Phase II and LTE studies indicated that the 10 mg BID dose (or corresponding mean Cmax, Cavg or Cmin) was estimated to have 1.3-1.9 times higher risk of serious infections compared to 5 mg BID (or corresponding mean Cmax, Cavg or Cmin).

Lipid changes: Increases in LDL-c following tofacitinib administration were described by an indirect response model. Mean steady state LDL-c increases are predicted to be reached in approximately 5 weeks. The final model estimates a steady-state ED50 of 3.6 mg suggesting that a dose of 5 mg BID tofacitinib reaches approximately the ED60, while 10 mg BID reaches approximately the ED75. Mean steady state was reached in 5 weeks.

Blood Pressure: In RA patients, a small statistically significant difference in mean SBP over placebo (0.30 and 0.60 mmHg for 5 and 10 mg BID, respectively) was predicted by the model. Differences in mean DBP were not significant. Based on 90% confidence intervals from the model, approximately 1.1 mmHg or greater mean increases in SBP and 0.6 mm Hg or greater mean increases in DBP at the 10 mg BID dose in RA patients could be excluded.

Haemoglobin: The Phase II study A3921025 suggested a dose-dependent effect on the reduction of Hb, however the pooled Phase II data did not show a consistent dose-dependent effect on Hb reduction.

ALT: The Phase II ALT population modelling studies clearly demonstrated an exposure related increase in mean ALT levels. This was observed for both monotherapy treatment and background DMARD studies.

Serum Creatinine: The exposure-response analyses utilized SCr levels pooled from five multi-center, doubleblind, placebo-controlled, parallel group studies in patients with RA. The final model estimates an ED50 of 0.88 mg suggesting that doses of 5 mg BID tofacitinib and greater are in excess of the ED80 (3.5 mg), resulting in similar predicted mean SCr increases for the 5 and 10 mg BID doses. Investigation of covariate effects indicated that Asians showed greater maximal increase (Emax) compared to non-Asians. The Applicant identified 12 outliers where this difference was greater than 6-times the model-predicted value.

Malignancy: Exposure-response analysis of data from patients who participated in the Phase II and LTE studies did not reveal an association between tofacitinib exposure (dose or subject-specific estimates of peak (MCmax), average (MCavg) or minimum (MCmin) concentrations) and risk of malignancy. The observations are contradictory to the renal transplant study (CP15 BD) in which a clear association between median exposure level of >125ng/mL was associated with increased incidence of PTLD. This is discussed further in the safety section.

2.4.3. Pharmacodynamics

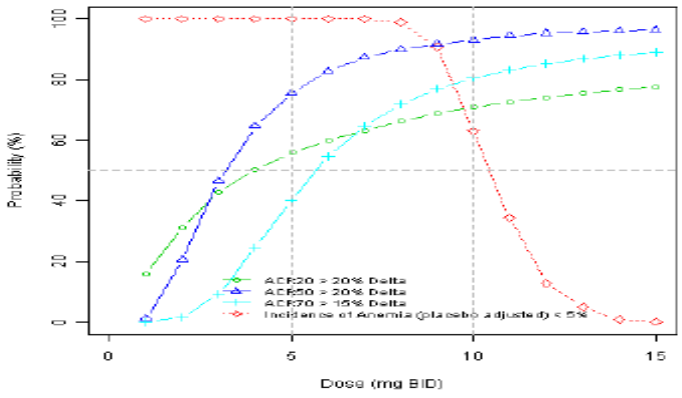
Mechanism of action

Tofacitinib is a potent inhibitor of the JAK kinase family. Although it inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2 in cellular studies, tofacitinib preferentially inhibits JAK1 and JAK3 dependent signalling with functional cellular selectivity over JAK2 homodimer signalling. 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.

Plasma concentration and effect:

Dose selection was primarily based on data from study A3921025, which assessed the probability of achieving a clinically meaningful target effect (PTE) values for ACR20, ACR50 and ACR70 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 inclusion of the 10mg dose was based on the possibility of increased benefit on ACR70 (PTE of 80% for the 10mg dose versus 40% for the 5 mg dose). The applicant's approach did not take into account other dose-limiting toxicities. In particular lymphopenia was not accounted for in the model.

Figure 1 **Probability of achieving target effects for efficacy (ACR20, ACR50 and ACR70 response rates) and safety (anemia) endpoints based on dose response modeling of A3921025 data**



Source: PMAR-00177

Pooled results from four Phase II studies showed evidence of dose response for each endpoint. Application of "Emax" models showed study specific differences in placebo response and maximum (Emax) drug effects, while the potency of tofacitinib, estimated as the dose providing half of the maximum effect (ED50), appeared to be comparable across the 4 studies. The point estimates (90% CI) for ED50 were 2.4 (1.4, 4.2) mg for ACR20, 4.8 (2.6, 8.8) mg for ACR50, 3.7 (1.6, 8.2) mg for ACR70 and 3.5 (2.3, 5.5) mg for mean DAS28-3(CRP) at Week 12. The two Phase II studies conducted in Japan (1039 and 1040) showed evidence of greater efficacy at the same dose level, raising the possibility of a greater pharmacodynamic effect in the Japanese population.

Primary and Secondary pharmacology

Primary pharmacology

Tofacitinib has been characterized in a series of assays dependent on JAK signaling. Human IL-2-dependent T cell proliferation (IC50 ~ 11 nM) and mixed lymphocyte assays (IC50 = 87 nM), primarily mediated by JAK3 and JAK1, were potently inhibited by tofacitinib. Tofacitinib inhibits IL-15 induced CD69 expression on natural killer (NK) cells (IC50 = 16 nM humans and 9.6 nM cynomolgus monkey) and CD8+ T cells (IC50 = 16 nM humans, 23 nM cynomolgus monkey)

JAK dependent cytokines are important in the differentiation of naïve T helper cells. When tested in differentiation assays, tofacitinib inhibited T-helper cell differentiation of naïve murine CD4+ T cells. Tofacitinib inhibited IL-4-dependent Th2 cell differentiation which could be attributed to inhibition of JAK1/3 downstream of IL-4R. Tofacitinib is a moderate inhibitor of JAK2. JAK2 is critical in erythrocyte maturation.

IL-12 dependent Th1 cell differentiation which requires enhancement by JAK1/JAK2 dependent IFNγ signaling is also blocked by tofacitinib. However, T-cell receptor (TCR) mediated proliferation was not affected in either case.

Th17 cells have been implicated in the pathology of RA. The effect of tofacitinib on Th17 differentiation was dependent on the cytokines used to promote differentiation. The combination of IL-23, IL-1β and IL-6 is thought to generate pathogenic Th17 cells. Tofacitinib inhibits IL–6 signaling and abrogates the expression of IL-23R and thus blocks the differentiation of Th17 cells.

Based on tofacitinib exposures relative to JAK IC50 for inhibition of various JAK dependent cytokines, tofacitinib is predicted to only partially inhibit JAK1 and JAK3 dependent signalling at efficacious concentrations over the day. This suggests that efficacy is derived from partial inhibition of multiple cytokine pathways such as the common γ chain cytokines, IFNα, IFNβ, IFNγ and IL-6 rather than complete inhibition of any one pathway.

Secondary pharmacology

JAK2 is important in erythrocyte maturation through EPO signalling. Based on the in vitro binding and functional assays and effects observed in the toxicology studies, JAK2 signalling could be affected by tofacitinib. To understand the effect of tofacitinib on circulating reticulocytes, EPO was administered to cynomolgus monkeys to stimulate erythropoiesis. Cynomolgus monkeys were orally dosed with 5 mg/kg tofacitinib or vehicle BID for 2 days prior and 14 days after a single subcutaneous (SC) injection of EPO (100 U/kg). Haematological observations (decreased reticulocytes, decreased red blood cell count and haemoglobin) persisted until Day 35 following EPO treatment. The haematological changes with tofacitinib treatment may be due to inhibition of signalling through JAK2 at Cmax = 382 ± 314 ng/mL and AUC(0-24) = 2980 ±558 ng•hr/mL.

Pharmacodynamic interactions with other medicinal products or substances

Study A3921109 was designed to generate lipid data to help characterize the magnitude of lipid elevations in patients with active RA treated with tofacitinib and to understand the effects of atorvastatin treatment on the lipid changes associated with tofacitinib (see clinical safety section).

Genetic differences in PD response

A comparison of the monotherapy dose response profiles of tofacitinib for ACR20, ACR50 and ACR70 endpoints between Japanese (Study A3921040) and non-Japanese (Study A3921035) RA patients to inform selection of equivalent doses for Japanese RA patients indicated that the ACR50 and ACR70 responses for 5 and 10 mg BID, when expressed as a percent of Emax, were similar between Japanese and non-Japanese RA patients, while ACR20 response appeared to be much higher in Japanese patients for 5 mg BID.

2.4.4. Discussion on clinical pharmacology

Tofacitinib is a potent inhibitor of JAK1/3 and a moderate inhibitor of JAK 2 pathways. The impact of these inhibitions is primarily on the immune system (T-cell function) and the haematological system. The non-clinical studies clearly demonstrated potent inhibition of T-cell proliferation/differentiation and effects on NK cells.

Dose selection was primarily based on study A39211025, with dose selection based driven by the parameters, ACR20, ACR50 and ACR70 for efficacy and changes in haemoglobin for safety. On this basis 5 mg and 10 mg were initially chosen to take forward into the phase III studies. No other safety parameters were considered in the dose selection. During the review the applicant has proposed to reduce the tofacitinib's dose to 5 mg administered twice daily.

The Applicant's exposure-response analysis of serum creatinine demonstrated a small, but drug-related impact. Given that RA patients were found to have a lower apparent oral clearance than healthy volunteers, extrapolations of dosage adjustment recommendations based on data in subjects without RA must be viewed with caution. In answer to questions regarding the recommended posology of tofacitinib in patients with reduced renal function and in patients undergoing dialysis, the applicant provided further analyses that showed that although tofacitinib CL/F is lower in RA patients compared to non-RA patients across the spectrum of CLcr values, the relative magnitude of impact of mild and moderate renal impairment is similar. Given the approximately 2-fold increase in tofacitinib AUC, the applicant proposed halving of the daily dose in RA patients (i.e. 5 mg QD) with severe renal impairment and this was is endorsed by the CHMP. Moreover the Applicant has proposed an update of the SmPC to indicate that supplemental doses are not necessary in patients undergoing dialysis because of the extensive non-renal clearance of tofacitinib. A statement indicating the magnitude of mean increase in tofacitinib AUC (approximately 40%) in subjects with end-stage renal disease (ESRD) compared to normal subjects has also been proposed to be added to the SmPC.

The applicant has also proposed to reduce the tofacitinib's dose to 5 mg once daily in patients with moderate hepatic impairment (Child-Pugh B) and in patients receiving potent inhibitors of cytochrome P450 which was endorsed by the CHMP.

The observation that the percentage of responders is higher for studies 1039/1040 both of which was conducted exclusively in the Japanese population raised the concern that there may be an enhanced pharmacodynamic effect of tofacitinib in the Asian population. Side effects like herpes, opportunistic infections and creatinine increases were also more common in Asians and this again raised the possibility of an exaggerated pharmacodynamic effect. The Population Modelling Analysis Report (PMAR) 00186 (Model-based Comparison of Dose-Response Profiles of tofacitinib in Japanese versus Western Rheumatoid Arthritis Patients) provided by the applicant showed that that further data are required to reach a definitive conclusion as in this analysis, study effect could not been distinguished from race effect (Japanese versus non-Japanese). The applicant proposed to amend the SmPC to mention that Asian patients have an increased risk of herpes zoster, opportunistic infections and interstitial lung disease and therefore, that tofacitinib should be used with caution in Asian patients. This was endorsed

by the CHMP.

Tofacitinib has 2 chiral centers at C3 and C4, with 4 possible stereoisomers. According to the applicant, among the four possible tofacitinib enantiomers 3R, 4R/ 3R, 4S/ 3S, 4S/ 3S, 4R, only the 3R, 4R enantiomer (the selected drug substance for Xeljanz) exhibits pharmacological activity. The statement regarding the pharmacological potency is based on binding capability to JAK receptors. Therefore, it could not be ruled out that, tofacitinib enantiomers 3R, 4S/ 3S, 4S/ 3S, 4R may interact with other receptors or tissue structures. In vitro investigations showed also that stereo-conversion occurs only under stressed oxidative conditions and unlikely to occur in vivo. This could not be endorsed by the CHMP as mechanisms of in vivo conversion are generally not fully elucidated and could not be easily predicted. Conclusively, conversion of tofacitinib needs to be confirmed by appropriate in vivo investigations. The Applicant clarified that the investigation of the activity of all 4 tofacitinib enantiomers, included binding to Janus kinase (JAK) receptors as well as a panel of 354 other kinases. The results demonstrated a high level of selectivity for the JAK family of kinases for each of these enantiomers, individually, indicating the safety profile of tofacitinib is unlikely to be related to off-target effects of the enantiomers. In addition, as only the 3R,4R enantiomer is present in the active pharmaceutical ingredient (API) and that in vivo conversion is unlikely, the Applicant considered that further characterization of tofacitinib enantiomers does not alter the assessment of the benefit/risk profile of tofacitinib as a product. The applicant proposed to confirm the theoretical and experimental evidence suggesting a low potential for stereo-conversion, in a post-approval commitment. The CHMP agreed that investigation of stereoconversion requires the development of suitable (qualified) analytical techniques and prior syntheses and/or purification process of enantiomers. However, such investigations should have been performed earlier as part of PK investigation of the drug. Considering that the analytical methods used in all PK studies are not stereo-selective, the information regarding the occurrence of stereo-conversion of the drug is crucial for the interpretation of the available PK data. The Applicant was advised to conduct a very limited investigation focusing only on the question of whether there is interconversion. The clinical samples to be tested can be limited to some time-points (tmax and later) in one repeated-dose study. Quantification of individual enantiomers would only be necessary in the event of interconversion.

2.4.5. Conclusions on clinical pharmacology

The applicant has conducted a thorough and high quality clinical pharmacology program and their conclusions are generally endorsed. As is the typical clinical pharmacology program, much of the understanding of the absorption and elimination mechanisms originates from studies in healthy volunteers and in vitro data.

The relative importance of renal and hepatic pathways to the overall elimination in rheumatoid arthritis (RA) patients appears to be similar to that in healthy volunteers. Therefore the clinical pharmacology data on renal and hepatic impairment and drug-drug interactions obtained in non-RA subjects can be extended to RA patients.

Renal secretory clearance does not represent a significant pathway of elimination for tofacitinib in healthy volunteers or RA patients and further elucidation of renal transporters for tofacitinib appears not necessary.With regards to dose-exposure relationships and safety, the CHMP noted a significant concern with regards to the exposure related effect of tofacitinib on white blood cell count, blood pressure, haemoglobin, LDL-c, creatinine and ALT observed in the phase 2 studies. This is further discussed in the safety section.

There is evidence of an exaggerated pharmacodynamic effect in Asian patients, both with regards to efficacy (studies 1039/1040) and safety (increased occurrence of AEs). In study PMAR-00186 it is

clearly stated that a difference in Emax was observed in the two studies analysed. However, in this analysis, it was not possible to distinguish study effect from race effect. Given the high incidence rates of ILD and opportunistic infections observed in Asian patients in the development programme and the literature evidence that suggests that Japanese patients may be more at risk of these AEs the applicant has updated the SmPC and RMP accordingly.

The applicant has proposed to reduce the tofacitinib dose to 5 mg once daily in in patient with severe renal impairment or severe hepatic impairment. However, this proposed reduction could be questionable in regard with the uncertainty in the knowledge about the beneficial effects of 5 mg BID dosing (see efficacy section).

The CHMP considers that the conduct a very limited investigation focusing only on the question of whether there is interconversion would have addressed the issues related to pharmacology. The clinical samples to be tested can be limited to some time points (tmax and later) in one repeated-dose study. Quantification of individual enantiomers would only be necessary in the event of interconversion.

2.5. Clinical efficacy

2.5.1. Dose response studies

The dose response relationship was assessed in 5 phase 2 studies, in diverse populations of DMARD inadequate responders, 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. Overall, in the Phase 2 development program, the efficacy of tofacitinib in RA patients was characterized over a dose range of 1 to 30 mg BID for durations ranging between 6 and 24 weeks in approximately 1560 patients.

The selection of the 5 and 10 mg BID doses of tofacitinib for the Phase 3 program was based primarily on dose-response modelling of safety and efficacy data observed in the A3921025 study. Efficacy results from phase 2 studies established a relationship between efficacy and dose. However, there is also a clear relationship between dose and AEs. Safety data from study 1025 were consistent with pivotal studies' findings. As compared with placebo, tofacitinib was associated with increased incidence of infections, gastro-intestinal disorders, respiratory adverse events, decreases in haemoglobin and neutrophils, increase in serum lipids and in serum creatinine levels.

2.5.2. Main studies

The demonstration of clinical efficacy was based on 5 clinical studies:

- Studies 1064 and 1044 to support the use in second line, with study 1044 to demonstrate the effect on structural damage.
- Study 1032 to support the use in third line indication (after failure to anti-TNF agents).
- Study 1046 to support the use in second and third line (after failure to traditional or biologic DMARD).
- Study 1045 to support the use in monotherapy for a second and third line.

For study details see Introduction to Clinical aspects.

<u>Study A3921064:</u> Phase 3 Randomized, Double-Blind, Active Comparator, Placebo-Controlled Study of the Efficacy and Safety of 2 Doses of tofacitinib in Patients with Active Rheumatoid Arthritis on Background Methotrexate.

Methods

Study 1064 was a phase 3 randomized, double-blind, active comparator (adalimumab), placebo-controlled, study of efficacy and safety data of 5 and 10 mg doses of tofacitinib in patients with active RA on background MTX. 700 patients were randomized in 5 treatment groups (tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo to tofacitinib 5 mg, placebo to tofacitinib 10 mg and ADA 40 mg eow). Study duration was one year, divided in 2 periods (DB, PC period of 3 to 6 months and DB extension period of 6 months). At month 3, the tender/painful and swollen joint counts were calculated and compared to the patient's individual Baseline values. If there was not a 20% improvement in both the tender/painful and swollen joint counts, the patient was considered a non-responder patient. If a non-responder patient was randomized to active treatment, he had to remain on the same treatment, at the same dose, for the duration of the study. If a non-responder patient was randomized to placebo, he switched to either tofacitinib 5 mg or 10 mg in a blinded manner for the remainder of the study. At the end of month 6, all patients were automatically advanced to their second predetermined treatment (double-blind, active-extension period).

Study Participants

To be eligible in the study, patients were required to have active RA on background MTX (either orally or parenterally). Main exclusion criteria included prior treatment to biologic DMARDs, active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB), history of malignancies or lymphoma, history of bacterial infections judged clinically significant by the investigator and history of herpes zoster or disseminated herpes simplex. These exclusion criteria are related to tofacitinib mechanism of action that acts as a potent immunosuppressive drug.

Treatments

Study medications were self-administered orally as 5 and 10 mg tablets BID. The ongoing ("background") DMARD was specified to be MTX (supplemented with folic acid) which must have been dosed orally or parenterally for at least 4 months and the dose stable for at least 6 weeks before the first dose of study drug and then remained stable during the study. Concomitant therapy with stably dosed "low dose" oral glucocorticoids (≤10 mg/d prednisone equivalent), NSAIDs, and specified analgesics was allowed.

Objectives

There were 4 primary objectives, to be assessed in the following sequence:

- Compare the efficacy of tofacitinib in doses of 5 and 10 mg BID versus placebo for the treatment of signs and symptoms of RA in patients with active RA on a stable background of MTX, as measured by ACR20 response rates at Month 6.

- Compare physical function status of patients after administration of 5 and 10 mg BID of tofacitinib versus placebo using the Health Assessment Questionnaire-Disability Index (HAQ-DI) at month 3 as compared to Baseline.

- Compare the rate of achieving Disease Activity Score (DAS)28-4 (erythrocyte sedimentation rate [ESR]) <2.6 at Month 6 after administration of 5 and 10 mg BID of tofacitinib versus placebo.

- To evaluate the safety and tolerability over 12 months of tofacitinib in doses of 5 and 10 mg BID versus placebo.

Secondary Objectives

- To compare the efficacy of oral tofacitinib in doses of 5 and 10 mg BID + MTX *versus* placebo + MTX for the treatment of signs and symptoms of RA at all other time points as measured by ACR20, ACR50, ACR70 and DAS28 response rates.

- To compare the efficacy of adalimumab 40 mg SC q 2 weeks versus placebo for the treatment of signs and symptoms in patients with active RA on a stable background of MTX at all time points as measured by ACR20, ACR50, ACR70, and DAS28 response rates.

- Durability of ACR20, ACR50, ACR70, and DAS28 response rates.

- Incidence of DAS28 remission and low disease activity state at each visit.

- Effects on all health outcomes measures in the study at each visit, as appropriate for the specific outcome, compared to Baseline.

- To estimate the efficacy of adalimumab 40 mg SC q 2 weeks versus tofacitinib in doses of 5 and 10 mg BID for the treatment of signs and symptoms in patients with active RA on a stable background of MTX at all time-points as measured by ACR20, ACR50, ACR70, and DAS28 response rates.

Outcomes/endpoints

The primary endpoints were, in order: Signs and symptoms as measured by ACR 20 at Month 6; Physical function as measured by the HAQ-DI change from baseline at Month 3; Incidence of DAS28-4 (ESR) <2.6 at Month 6.

Secondary endpoints included the following, ACR20 Responder rate at times other than Month 6; ACR50 Responder rate; ACR70 Responder rate; Actual and change from Baseline of the 7 individual components (tender joint count, swollen joint count, patient assessment of arthritis pain, physician global assessment of arthritis, patient global assessment of arthritis, C-Reactive Protein (CRP) and HAQ-DI) of the ACR criteria variables (separate analyses); Actual and change from Baseline in DAS28 which included the following 4 different DAS: DAS using [DAS28-3(CRP) and DAS28-4(CRP)] and DAS using Erythrocyte Sedimentation Rate [DAS28-3(ESR) and DAS28-4(ESR)].

Sample size

The protocol was designed to address objectives based on 3 primary endpoints. In order to preserve type I error, each endpoint was assessed sequentially using gate-keeping or a step-down approach where statistical significance could be claimed for the second endpoint only if the first endpoint in the sequence met the requirements for significance. Additionally, as there were 2 doses within each endpoint, the gate-keeping or step-down approach was also applied, i.e., the high dose (tofacitinib 10 mg BID) at a given endpoint could achieve significance only if the high dose at the prior endpoint was significant; the low dose (tofacitinib 5 mg BID) at a given endpoint could achieve significance only if both the high dose at the same endpoint and the low dose at the prior endpoint were significant.

For each endpoint, and for each dose group, the comparison with placebo was conducted using a significance level (alpha) set at 0.05 (2-sided) or equivalently 0.025 (1-sided). For the ACR20 analysis, this sample size was planned to yield over 90% power, assuming a difference in response rates of at least 20% (with the placebo response at 30%). For the analysis of the HAQ-DI, the sample size resulted in over 90% power for differences of 0.3 or greater, assuming a standard deviation of 0.75.

Randomisation

At the study site, randomization of patients was accomplished using an interactive voice response system (IVRS), an automated web/telephone randomization system provided by the sponsor. Seven hundred

and seventeen (717) patients were randomized in a 4:4:1:1:4 ratio to 1 of the 5 parallel treatment sequences for the 2 periods (double-blind, placebo-controlled period, then double-blind, active-extension period).

Blinding (masking)

This study was patient, investigator and sponsor-blinded.

Statistical methods

The full analysis set (FAS) included all patients who were randomized to the study and received at least 1 dose of the randomized study drug (tofacitinib, adalimumab, or placebo). The primary analysis population for this study was defined by the FAS. Patients must have had at least 1 postbaseline measurement in order to appear in any of the analyses of the FAS data sets. FAS patients who had a protocol deviation thought to affect the efficacy analysis were excluded from the per-protocol (PP) efficacy analysis. Protocol deviations that would have excluded patients from the PP set were defined before the randomization blind was broken. The safety analysis set was defined as those patients who received at least 1 dose of the study drug (tofacitinib, adalimumab, or placebo).

Analyses of the three primary endpoints were based on the FAS. For ACR20 and Incidence of DAS28-4(ESR) <2.6 at Month 6, the normal approximation for the difference in binomial proportions was used.

For the change from Baseline in the HAQ-DI at Month 3, the mixed-effect model with repeated measures was used.

Results

Participant flow

Table 34

Number (%) of Patients	CP-690,550 5 mg	CP-690,550 10 mg	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID	Adalimumab 40 mg SC q 2 weeks
Screened: 1042					
Assigned to study treatment	204	201	56	52	204
Treated	204	201	56	52	204
Completed	150 (73.5)	158 (78.6)	47 (83.9)	39 (75.0)	162 (79.4)
Discontinued	54 (26.5)	43 (21.4)	9 (16.1)	13 (25.0)	42 (20.6)
Patient died	0	0	0	0	1 (0.5)
Related to study drug	25 (12.3)	22 (10.9)	5 (8.9)	5 (9.6)	22 (10.8)
Adverse event	19 (9.3)	15 (7.5)	2 (3.6)	2 (3.8)	16 (7.8)
Lack of efficacy	6 (2.9)	7 (3.5)	3 (5.4)	3 (5.8)	6 (2.9)
Not related to study drug	29 (14.2)	21 (10.4)	4 (7.1)	8 (15.4)	19 (9.3)
Adverse event	5 (2.5)	9 (4.5)	0	3 (5.8)	6 (2.9)
Lost to follow-up	2 (1.0)	1 (0.5)	0	0	0
Other	18 (8.8)	9 (4.5)	4 (7.1)	4 (7.7)	12 (5.9)
Patient no longer willing to participate in study	4 (2.0)	2 (1.0)	0	1 (1.9)	1 (0.5)

Recruitment

First Subject First Visit: 20 May 2009
Last Subject Last Visit: 10 March 2011

Conduct of the study

Table 35 A3921064 Protocol Deviation Summary Table

	Placebo/ CP-690,550 5 mg BID	Placebo/ CP-690,550 10 mg BID	CP-690,550 5 mg BID/ CP-690,550 5 mg BID	CP-690,550 10 mg BID/ CP-690,550 10 mg BID	Adalimumab 40 mg q2wkSC/ Adalimumab 40 mg q2wkSC	Screen Failure	Total
Concomitant Medication*	5	2	13	9	13	1	**43**
Inclusion/Exclusion Criteria	7	10	23	27	34	10	**111**
Informed Consent	7	9	17	21	21	16	**91**
Investigational Product**	7	8	33	26	21	0	**95**
Laboratory	12	10	36	38	31	1	**128**
Procedures/Tests	12	16	76	75	91	4	**274**
Protocol Specific Discontinuation Criteria	0	0	2	1	0	0	**3**
Randomization	0	0	0	0	0	1	**1**
Safety Reporting	0	0	2	1	1	0	**4**
Visit Schedule	1	1	8	6	5	0	**21**
Grand Total	**51**	**56**	**210**	**204**	**217**	**33**	**771**

**Concomitant medications include prohibited medications and rescue errors affecting the efficacy of primary endpoints before month 6.*
*** Investigational product includes advancement errors and interrupting study medication before month 6.*
Source: Appendix 1 Table 16.2.2a Protocol Deviations with Drug Assignment for A3921064
Abbreviations: BID=twice a day, mg=milligram, , q2wk=every 2 weeks SC= subcutaneous

Baseline data

Table 36 Baseline Characteristics

Baseline Characteristic Parameter	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID	Adalimumab 40 mg SC q 2 weeks
Disease duration (rheumatoid arthritis) (duration since first diagnoses, years):					
N	204	201	56	52	204
Mean	7.6	7.4	6.9	9.0	8.1
Range	0.3-39.0	0.3-49.0	0.3-40.0	0.3-49.4	0.2-36.3
Rheumatoid factor, n (%):					
N	199	198	56	51	201
Negative	66 (33.17)	67 (33.84)	16 (28.57)	20 (39.22)	64 (31.84)
Positive	133 (66.83)	131 (66.16)	40 (71.43)	31 (60.78)	137 (68.16)
Anti-CCP, n (%):					
N	202	197	55	50	202
Negative	58 (28.71)	71 (36.04)	13 (23.64)	19 (38.00)	51 (25.25)
Positive	144 (71.29)	126 (63.96)	42 (76.36)	31 (62.00)	151 (74.75)
DAS28-3(CRP)					
N	200	199	55	51	201
Mean (SD)	5.43 (0.89)	5.43 (0.83)	5.55 (0.95)	5.32 (0.79)	5.33 (0.92)
Range	2.08-7.18	3.10-7.58	3.72-7.34	3.81-6.72	2.39-7.30
DAS28-4(ESR):					
N	193	194	54	49	194
Mean (SD)	6.56 (0.89)	6.52 (0.84)	6.60 (1.04)	6.44 (0.73)	6.38 (0.87)
Range	3.21-8.42	4.16-9.01	4.11-8.50	5.08-7.82	3.56-8.81
HAQ-DI:					
N	201	199	55	51	201
Mean (SD)	1.50 (0.64)	1.53 (0.63)	1.47 (0.68)	1.36 (0.68)	1.50 (0.59)
Range	0.00-3.00	0.00-3.00	0.13-3.00	0.00-3.00	0.00-2.75
Tender joint counts:					
N	201	199	55	51	201
Mean (SD)	28.48 (15.03)	26.09 (14.13)	26.58 (14.36)	28.10 (14.43)	26.65 (15.34)
Range	0.00-68.00	6.00-66.00	9.00-68.00	7.00-60.00	6.00-67.00
Swollen joint counts:					
N	201	199	55	51	201
Mean (SD)	16.66 (8.76)	15.80 (7.82)	16.93 (9.98)	16.37 (7.51)	16.35 (8.65)
Range	0.00-54.00	6.00-48.00	6.00-58.00	6.00-34.00	6.00-50.00
ESR (mm/hr):					
N	195	194	55	49	194
Mean (SD)	48.56 (23.88)	49.90 (25.94)	52.65 (26.07)	42.88 (19.37)	48.48 (23.92)
Range	2.00-121.00	8.00-145.00	6.00-130.00	14.00-122.00	9.00-130.00
CRP (mg/L):					
N	200	199	56	51	201
Mean (SD)	14.89 (18.58)	17.27 (19.52)	20.29 (20.07)	11.57 (16.25)	17.48 (22.48)
Range	0.20-142.00	0.30-99.10	0.77-79.00	0.31-92.40	0.20-171.00

Source: Tables 14.1.2.2, 14.1.2.1.3, 14.1.2.1.4, 14.2.4.2, 14.2.5.2, 14.2.6.2, 14.2.7.2, 14.2.11.2, 14.2.12.2, 14.2.13.2
Abbreviations: BID = twice daily; CCP = cyclic citrullinated peptide; CRP = C-reactive protein; DAS = Disease Activity Score; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire - Disability Index; N = number of patients; n = number of patients meeting prespecified criteria; q = every; SC = subcutaneous; SD = standard deviation.

Numbers analysed

Table 37

Number (%) of Patients:	CP-690,550 5 mg	CP-690,550 10 mg	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID	Adalimumab 40 mg SC q 2 weeks
Assigned to study treatment	204	201	56	52	204
Treated	204	201	56	52	204
Completed	150 (73.5)	158 (78.6)	47 (83.9)	39 (75.0)	162 (79.4)
Discontinued	54 (26.5)	43 (21.4)	9 (16.1)	13 (25.0)	42 (20.6)
Analyzed for efficacy:					
Full analysis Set	201 (98.5)	199 (99.0)	56 (100.0)	51 (98.1)	201 (98.5)
Per protocol analysis set	187 (91.7)	188 (93.5)	53 (94.6)	45 (86.5)	192 (94.1)
Analyzed for safety:					
Adverse events	204 (100.0)	201 (100.0)	56 (100.0)	52 (100.0)	204 (100.0)
Laboratory data	203 (99.5)	201 (100.0)	56 (100.0)	49 (94.2)	204 (100.0)

Outcomes and estimation

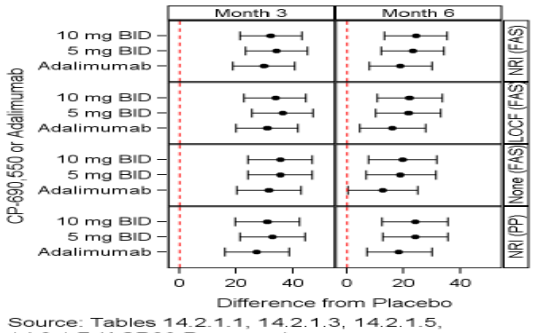
Primary endpoints

ACR 20 responses rates at month 6

Table 38. Normal Approximation to ACR20 Reponses Rates at Month 6 (FAS, NRI, Difference from placebo)

				Difference From Placebo			
					95% CI for Difference		
Treatment	**N**	**n**	**%**	**Difference**	**Lower**	**Upper**	**P-Value**
Tofacitinib 5 mg BID	**196**	**101**	**51.53**	**23.22**	**12.16**	**34.29**	**<0.001**
Tofacitinib 10 mg BID	**196**	**103**	**52.55**	**24.24**	**13.18**	**35.31**	**<0.001**
Placebo	**106**	**30**	**28.3**				

Figure 2 **Differences From Placebo in Response Rates (%) and 95% Confidence Intervals for ACR20 at Months 3 and 6 (Sensitivity Analyses)**



Source: Tables 14.2.1.1, 14.2.1.3, 14.2.1.5, 14.2.1.7 (ACR20 Response)

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; LOCF=last observation carried forward; None=no imputation; NRI=nonresponder imputation; PP=per protocol.

HAQ-DI at month 3

Table 39. Summary of LS mean Changes From baseline in HAQ-DI at Month 3 (FAS, Differences From Placebo)

			Difference From Placebo			
				95% CI for Difference		
Treatment	N	LS Mean	LS Mean Difference	Lower	Upper	P-Value
Tofacitinib 5 mg BID	188	-0.55	-0.31	-0.43	-0.19	<0.001
Tofacitinib 10 mg BID	185	-0.61	-0.38	-0.50	-0.25	<0.001
Placebo	98	-0.24				

Table 40 - DAS28(ESR)<2.6 at month 6

				Difference From Placebo			
					95% CI for Difference		
Treatment	N	n	%	Difference	Lower	Upper	P-Value
Tofacitinib 5 mg BID	177	13	7.34	6.25	1.86	10.64	<0.001
Tofacitinib 10 mg BID	176	22	12.50	11.41	6.08	16.73	<0.001
Placebo	92	1	1.09				

Secondary endpoints and comparison with Adalimumab

Table 41. ACR20, ACR50, and ACR70 Response Rates at Month 3 and Month 6 (FAS, NRI, Difference from Adalimumab) – Study A3921064

Treatment	N	n	%	Difference from Adalimumab			
				Difference	95% CI for Difference		P- Value
					Lower	Upper	
ACR20							
Month 3							
tofacitinib 5 mg BID	196	119	60.71	4.43	-5.27	14.14	0.3708
tofacitinib 10 mg BID	196	115	58.67	2.39	-7.35	12.14	0.6305
Adalimumab 40 mg SC QOW	199	112	56.28				
Month 6							
tofacitinib 5 mg BID	196	101	51.53	4.29	-5.55	14.14	0.3929
tofacitinib 10 mg BID	196	103	52.55	5.31	-4.53	15.16	0.2901
Adalimumab 40 mg SC QOW	199	94	47.24				
ACR50							
Month 3							
tofacitinib 5 mg BID	196	67	34.18	10.56	1.68	19.44	0.0197
tofacitinib 10 mg BID	196	54	27.55	3.93	-4.66	12.53	0.370
Adalimumab 40 mg SC QOW	199	47	23.62				
Month 6							
tofacitinib 5 mg BID	196	72	36.73	9.09	-0.07	18.27	0.0519
tofacitinib 10 mg BID	196	68	34.69	7.05	-2.05	16.16	0.129
Adalimumab 40 mg SC QOW	199	55	27.64				
ACR70							
Month 3							
tofacitinib 5 mg BID	196	24	12.24	3.7	-2.3	9.71	0.2274
tofacitinib 10 mg BID	196	29	14.80	6.25	-0.05	12.56	0.0520
Adalimumab 40 mg SC QOW	199	17	8.54				
Month 6							
tofacitinib 5 mg BID	196	39	19.90	10.85	3.98	17.71	0.0019
tofacitinib 10 mg BID	196	43	21.94	12.89	5.86	19.92	0.0003
Adalimumab 40 mg SC QOW	199	18	9.05				

Table 42. Summary of LS Mean Changes from Baseline in HAQ-DI at month 3 (FAS, Differences from Adalimumab) – Study A3921064

Treatment	N	LS Mean	Difference From Adalimumab		
			LS Mean Difference	95% CI for Difference	P- Value
tofacitinib 5 mg BID	188	-0.55	-0.06	(-0.16, 0.04)	0.2609
tofacitinib 10 mg BID	185	-0.61	-0.12	(-0.23, -0.02)	0.0157
Adalimumab 40 mg SC QOW	190	-0.49			

Table 43. Summary of Patients Achieving DAS28-4(ESR) <2.6 (FAS, NRI, Comparisons to Adalimumab) at month 6 – Study A3921064

				Difference from Adalimumab		
	N	n	Proportion (%)	Difference	95% Confidence Interval	p-value
tofacitinib 5 mg BID	177	13	7.34	1.16	(-4.05, 6.38)	0.662
tofacitinib 10 mg BID	176	22	12.5	6.32	(0.28, 12.35)	0.040
Adalimumab 40 mg SC QOW	178	11	6.18			

Study A3921045: Phase 3, Randomized, Double Blind, Placebo Controlled Study of the Efficacy and Safety of 2 Doses of tofacitinib Monotherapy in Patients with Active Rheumatoid Arthritis

Methods

Study 1045 was a phase 3, randomized, 6-month, double-blind, placebo-controlled, monotherapy study with RA patients who had an inadequate response to at least 1 DMARD (traditional or biologic). Six hundred and eleven patients were randomized to 4 treatment groups (tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo BID → tofacitinib 5 mg BID at Month 3 or placebo BID → tofacitinib 10 mg BID at month 3). Since patients enrolled in this study were not on background MTX, patients who were randomized to placebo began receiving tofacitinib in a blinded fashion at either 5 mg or 10 mg at month 3, for the remainder of the 6-month study.

Study Participants

Patients were required to have active RA with stable antimalarials for at least 8 weeks before the first dose of study drug. No other DMARDs (traditional or biologic) were allowed as concomitant therapy during the study. All other DMARDs (traditional and biologic) were required to be washed out before study entry. Exclusionary criteria included active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB), history of malignancies or lymphoma, history bacterial infections judged clinically significant by the investigator and history of herpes zoster or disseminated herpes simplex. These exclusion criteria were in relation to the mechanism of action of Tofacitinib that acts on a potent immunosuppressive drug.

Treatments

Study medications were self-administered orally as 5 and 10 mg tablets BD. Only ongoing ("background") antimalarials were allowed. Concomitant therapy with stably dosed "low dose" oral glucocorticoids (≤10 mg/d prednisone equivalent), NSAIDs, and specified analgesics was allowed.

Objectives

Primary Objectives

- Compare the efficacy of tofacitinib, as monotherapy, in doses of 5 mg twice daily (BID) and 10 mg BID versus placebo in patients with RA who have had an inadequate response to a DMARD (traditional or biologic), as measured by ACR20 response rates at month 3.
- Compare physical function status of patients with active RA after administration of tofacitinib as monotherapy in tofacitinib doses of 5 mg and 10 mg BID versus placebo, as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) response at month 3.

- Compare the rate of achieving Disease Activity Score (DAS)28-4 <2.6 at Month 3 in patients with active RA after administration of tofacitinib as monotherapy in tofacitinib doses of 5 mg and 10 mg BID versus placebo.
- Compare the safety of 2 doses of tofacitinib monotherapy versus placebo

Outcomes/endpoints

Primary and secondary endpoints were the same than those used in study 1064 but ACR 20 response rate and DAS 28 were assessed at month 3 instead of month 6 (due to ethical reason since patients were not received background MTX).

Sample size

The study was designed to address the primary study objectives based on 3 primary endpoints. In order to preserve type I error, each objective was assessed sequentially, using a gate-keeping or step-down approach, where statistical significance could be claimed for the endpoint only if the previous endpoint in the sequence met the requirements for significance. Additionally, as there were 2 doses within each endpoint, the gate-keeping or step-down approach was to be applied, i.e., the highest dose (tofacitinib 10 mg BID) at a given endpoint could achieve significance only if the 5 mg BID dose at the prior endpoint was significant.

For each endpoint and for each dose, the comparison with placebo was conducted using a significance level (alpha) set at 0.05 (2-sided) or equivalently 0.025 (1-sided).

For the ACR20 analysis, this sample size was planned to yield over 90% power, assuming a difference in response rates of at least 20% (with the placebo response at 30%). For the analysis of the HAQ-DI, the sample size resulted in over 90% power (90.3%) for differences of 0.3 or greater, assuming a standard deviation of 0.75. For the analysis of DAS28-4(ESR) <2.6, this sample size resulted in over 90% power (93.6%) for differences in response rates of at least 15% (with placebo response at 10%).

Randomisation

At the study site, randomization of patients was accomplished using an interactive voice response system (IVRS), an automated web/telephone randomization system provided by the sponsor. Six hundred eleven patients (611) patients were randomized in a 4:4:1:1 ratio to one of the following sequences, respectively: 1) tofacitinib 5 mg BID, 2) tofacitinib 10 mg BID, 3) placebo →tofacitinib 5 mg BID, and 4) placebo →tofacitinib 10 mg BID. Because patients enrolled in this study were not receiving background methotrexate (MTX), patients randomized to the placebo sequences were advanced at Month 3 to active treatment with 5 mg BID or 10 mg BID of tofacitinib in a blinded manner. This advancement scheme limited the time patients were on placebo without DMARD therapy to 12 weeks.

Blinding (masking)

This study was patient, investigator and sponsor-blinded.

Statistical methods

The same statistical method as study 1064 was used (with a step down approach for each endpoint). Analysis sets and handling of missing data were also similar to study 1064. The primary analysis population for this study was also defined by the FAS.

Results

Participant flow

Table 44 **Patient Disposition**

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Screened: 954				
Assigned to Study Treatment	244	245	61	61
Treated	243[a]	245	61	61
Completed	232 (95.1)	218 (89.0)	54 (88.5)	51 (83.6)
Discontinued	11 (4.5)	27 (11.0)	7 (11.5)	10 (16.4)
Patient Died	0	1 (0.4)[b]	0	0
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)
Not Related to Study Drug	7 (2.9)	19 (7.8)	2 (3.3)	5 (8.2)
Adverse event	0	3 (1.2)	1 (1.6)	1 (1.6)
Other	1 (0.4)	2 (0.8)	0	1 (1.6)
Protocol violation	2 (0.8)	8 (3.3)	1 (0.4)	1 (1.6)
Patient no longer willing to participate in study	4 (1.6)	6 (2.4)	0	2 (3.3)

Recruitment

First Subject First Visit: 09 February 2009
Last Subject Last Visit: 23 June 2010

Conduct of the study

Table 45 **A3921045 Protocol Deviation Summary Table**

	Placebo/ CP-690,550 5 mg BID	Placebo/ CP-690,550 10 mg BID	CP-690,550 5 mg BID/ CP-690,550 5 mg BID	CP-690,550 10 mg BID/ CP-690,550 10 mg BID	Screen Failure	Total
Concomitant Medication	5	9	18	19	0	**51**
Inclusion/Exclusion Criteria	3	8	12	10	1	**34**
Informed Consent	3	7	12	13	8	**43**
Investigational Product	5	13	27	31	0	**76**
Laboratory	12	4	20	17	0	**53**
Other	5	1	9	7	0	**22**
Procedures/Tests	10	32	99	73	0	**214**
Protocol Specific Discontinuation Criteria	0	0	1	2	0	**3**
Randomization	0	1	2	2	0	**5**
Safety Reporting	0	1	1	1	0	**3**
Visit Schedule	6	6	26	22	0	**60**
Grand Total	**49**	**82**	**227**	**197**	**9**	**564**

**Concomitant medications include prohibited medications and rescue errors affecting the efficacy of primary endpoints before month 3.*
*** Investigational product includes advancement errors and interrupting study medication before month 3.*
Source: Appendix 4 Table 16.2.2a Protocol Deviations with Drug Assignment for A3921045
Abbreviations: BID=twice a day, mg=milligram

Baseline data

Table 46 Baseline Characteristics

Baseline Characteristic Parameter	CP-690,550 5 mg BID N=243 n (%)	CP-690,550 10 mg BID N=245 n (%)	Placebo → CP-690,550 5 mg BID N=61 n (%)	Placebo → CP-690,550 10 mg BID N=61 n (%)
Disease duration (rheumatoid arthritis) (duration since first diagnoses, years):				
Mean	8.0	8.6	7.3	8.1
Range	0.2-42.3	0.2-49.0	0.3-28.0	0.1-28.0
Rheumatoid factor:				
Negative	69 (28.75)	84 (34.85)	26 (42.62)	32 (52.46)
Positive	171 (71.25)	157 (65.15)	35 (57.38)	29 (47.54)
Anti-CCP:				
Negative (<20 units)	70 (28.93)	75 (30.74)	17 (27.87)	27 (45.0)
Weak positive (20-39 units)	12 (4.96)	12 (4.92)	3 (4.92)	3 (5.00)
Moderate positive (40-59 units)	8 (3.31)	5 (2.05)	1 (1.64)	0
Strong positive (≥60 units)	152 (62.81)	152 (62.30)	40 (65.57)	30 (50.00)
DAS28-3(CRP):				
Mean (SD)	5.68 (0.90)	5.60 (0.91)	5.57 (0.76)	5.56 (0.94)
Range	3.21-7.90	3.22-7.75	4.01-7.38	3.11-7.91
DAS28-4(ESR):				
Mean (SD)	6.71 (0.91)	6.67 (0.91)	6.59 (0.83)	6.67 (1.06)
Range	3.56-8.56	4.40-8.61	4.14-8.42	4.49 (8.94)
HAQ-DI:				
Mean (SD)	1.53 (0.66)	1.50 (0.64)	1.48 (0.61)	1.58 (0.69)
Range	0.0-3.0	0.0-3.0	0.1-2.8	0.0-3.0
Tender joint counts:				
Mean (SD)	29.42 (14.98)	29.10 (15.59)	28.39 (15.31)	29.39 (16.59)
Range	6.0-68.0	6.0-68.0	8.0-68.0	5.0-67.0
Swollen joint counts:				
Mean (SD)	16.28 (8.58)	17.03 (10.38)	16.84 (9.96)	17.69 (11.53)
Range	5.0-59.0	1.0-63.0	4.0-50.0	2.0-57.0
ESR (mm/Hr):				
Mean (SD)	52.99 (27.52)	52.12 (27.03)	47.43 (25.04)	54.39 (33.80)
Range	5.0-130.0	6.0-160.0	5.0-108.0	3.0-141.0
CRP (mg/L):				
Mean (SD)	22.75 (27.00)	19.00 (19.85)	14.06 (12.99)	21.50 (32.66)
Range	0.2-137.0	0.2-113.0	0.2-45.6	0.3-153.0

Source: Tables 14.1.2.1.3, 14.1.2.1.4, 14.1.2.2, 14.2.6.1.2, 14.2.7.1.2, 14.2.8.1.2, 14.2.9.1.2, 14.2.13.1.2, 14.2.14.1.2, and 14.2.15.1.2

Abbreviations: BID = twice daily, CCP = cyclic citrullinated peptide, CRP = C-reactive protein, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, HAQ-DI = Health Assessment Questionnaire - Disability Index, N = number of patients, n = number of patients meeting prespecified criteria, SD = standard deviation

Numbers analysed

Table 47

No. (%) of Patients	CP-690,550 5 mg BID n (%)	CP-690,550 10 mg BID n (%)	Placebo → CP-690,550 5 mg BID n (%)	Placebo → CP-690,550 10 mg BID n (%)
Assigned to Study Treatment	244	245	61	61
Treated	243[a]	245	61	61
Completed	232 (95.1)	218 (89.0)	54 (88.5)	51 (83.6)
Discontinued	11 (4.5)	27 (11.0)	7 (11.5)	10 (16.4)
Analyzed for Efficacy:				
Full Analysis Set	241 (98.8)	243 (99.2)	61 (100.0)	61 (100.0)
Per Protocol Analysis Set	205 (84.0)	201 (82.0)	50 (82.0)	45 (73.8)
Analyzed for Safety:				
Adverse events	243 (99.6)	245 (100.0)	61 (100.0)	61 (100.0)
Laboratory data	243 (99.6)	245 (100.0)	60 (98.4)[b]	61 (100.0)

Outcomes and estimation

Primary endpoints

1. **ACR20 responses rates at month 3**

Table 48 Normal Approximation to ACR20 Response Rates at Month 3 (FAS, NRI, Difference From Placebo)

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

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

2. **Changes From Baseline in HAQ-DI at Month 3**

Table 49 Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, Differences From Placebo)

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

Source: Table 14.2.1.2
Abbreviations: BID = twice daily, CI = confidence interval, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire - Disability Index, LS = least squares, N = number of subjects

3. **Rate of Patients Achieving DAS28-4(ESR) <2.6 Versus Placebo at Month 3**

Table 50 Summary of Patients Achieving DAS28-4(ESR) <2.6 at Month 3 (FAS, No Imputation, Comparisons to Placebo)

Treatment	N	n	%	Comparison to Placebo			
				Difference	95% CI for Difference		P-value
					Lower	Upper	
CP-690,550 5 mg BID	229	14	6.11	1.31	-3.85	6.46	0.6193
CP-690,550 10 mg BID	219	22	10.05	5.24	-0.49	10.96	0.0728
Placebo	104	5	4.81	Not applicable			

Source: Table 14.2.15.12.1
Abbreviations: BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, CI = confidence interval

Secondary endpoints

ACR 20 response at month 6

At month 6, response rates for patients in the tofacitinib 5 mg and 10 mg groups were 69.3% and 71.1%, respectively, compared with 58.3% and 56.7% for patients in the placebo → tofacitinib 5 mg and placebo → tofacitinib 10 mg groups, respectively. The tofacitinib 10 mg treatment sequence had higher response rates than the tofacitinib 5 mg group.

ACR 50 response at months 3 and 6

Table 51

Normal Approximation to ACR 50 Response Rates per Visit (PAS, NRI), Comparisons within Sequence

		N	n	PERCENT	STD ERR	Z Value	95% CONFIDENCE LOWER	95% CONFIDENCE UPPER	P-VALUE
WEEK 2(NRI)	CP-690,550 5 mg BID	240	14	5.83	1.51	3.86	2.87	8.80	0.0001
	CP-690,550 10 mg BID	240	31	12.92	2.16	5.97	8.67	17.16	<0.0001
	Placebo -> 5 mg BID	59	3	5.08	2.86	1.78	-0.52	10.69	0.0754
	Placebo -> 10 mg BID	60	2	3.33	2.32	1.44	-1.21	7.88	0.1503
MONTH 1(NRI)	CP-690,550 5 mg BID	241	42	17.43	2.44	7.13	12.64	22.22	<0.0001
	CP-690,550 10 mg BID	242	58	23.97	2.74	8.73	18.59	29.35	<0.0001
	Placebo -> 5 mg BID	60	3	5.00	2.81	1.78	-0.51	10.51	0.0756
	Placebo -> 10 mg BID	60	2	3.33	2.32	1.44	-1.21	7.88	0.1503
MONTH 2(NRI)	CP-690,550 5 mg BID	241	63	26.14	2.83	9.24	20.59	31.69	<0.0001
	CP-690,550 10 mg BID	242	82	33.88	3.04	11.14	27.92	39.85	<0.0001
	Placebo -> 5 mg BID	60	5	8.33	3.57	2.34	1.34	15.33	0.0195
	Placebo -> 10 mg BID	60	2	3.33	2.32	1.44	-1.21	7.88	0.1503
MONTH 3(NRI)	CP-690,550 5 mg BID	241	75	31.12	2.98	10.43	25.27	36.97	<0.0001
	CP-690,550 10 mg BID	242	89	36.78	3.10	11.86	30.70	42.85	<0.0001
	Placebo -> 5 mg BID	60	9	15.00	4.61	3.25	5.96	24.04	0.0011
	Placebo -> 10 mg BID	60	6	10.00	3.87	2.58	2.41	17.59	0.0098
MONTH 4(NRI)	CP-690,550 5 mg BID	241	90	37.34	3.12	11.99	31.24	43.45	<0.0001
	CP-690,550 10 mg BID	242	104	42.98	3.18	13.50	36.74	49.21	<0.0001
	Placebo -> 5 mg BID	60	17	28.33	5.82	4.87	16.93	39.74	<0.0001
	Placebo -> 10 mg BID	60	17	28.33	5.82	4.87	16.93	39.74	<0.0001
MONTH 5(NRI)	CP-690,550 5 mg BID	241	95	39.42	3.15	12.52	33.25	45.59	<0.0001
	CP-690,550 10 mg BID	242	110	45.45	3.20	14.20	39.18	51.73	<0.0001
	Placebo -> 5 mg BID	60	22	36.67	6.22	5.89	24.47	48.86	<0.0001
	Placebo -> 10 mg BID	60	21	35.00	6.16	5.68	22.93	47.07	<0.0001
MONTH 6(NRI)	CP-690,550 5 mg BID	241	101	41.91	3.18	13.19	35.68	48.14	<0.0001
	CP-690,550 10 mg BID	242	113	46.69	3.21	14.56	40.41	52.98	<0.0001
	Placebo -> 5 mg BID	60	20	33.33	6.09	5.48	21.41	45.26	<0.0001
	Placebo -> 10 mg BID	60	20	33.33	6.09	5.48	21.41	45.26	<0.0001

Table 52- ACR 70 response at months 3 and 6

Table 14.2.5.1.2
CP-690,550 Protocol A3921045
Normal Approximation to ACR 70 Response Rates per Visit (PAS, NRI), Comparisons within Sequence

		N	n	PERCENT	STD ERR	Z Value	95% CONFIDENCE LOWER	95% CONFIDENCE UPPER	P-VALUE
WEEK 2(NRI)	CP-690,550 5 mg BID	240	5	2.08	0.92	2.26	0.28	3.89	0.0238
	CP-690,550 10 mg BID	240	11	4.58	1.35	3.40	1.94	7.23	0.0007
	Placebo -> 5 mg BID	59	0	0.00					
	Placebo -> 10 mg BID	60	0	0.00					
MONTH 1(NRI)	CP-690,550 5 mg BID	241	12	4.98	1.40	3.55	2.23	7.73	0.0004
	CP-690,550 10 mg BID	242	22	9.09	1.85	4.92	5.47	12.71	<0.0001
	Placebo -> 5 mg BID	60	1	1.67	1.65	1.01	-1.57	4.91	0.3132
	Placebo -> 10 mg BID	60	1	1.67	1.65	1.01	-1.57	4.91	0.3132
MONTH 2(NRI)	CP-690,550 5 mg BID	241	24	9.96	1.93	5.16	6.18	13.74	<0.0001
	CP-690,550 10 mg BID	242	46	19.01	2.52	7.54	14.06	23.95	<0.0001
	Placebo -> 5 mg BID	60	3	5.00	2.81	1.78	-0.51	10.51	0.0756
	Placebo -> 10 mg BID	60	1	1.67	1.65	1.01	-1.57	4.91	0.3132
MONTH 3(NRI)	CP-690,550 5 mg BID	241	37	15.35	2.32	6.61	10.80	19.90	<0.0001
	CP-690,550 10 mg BID	242	49	20.25	2.58	7.84	15.18	25.31	<0.0001
	Placebo -> 5 mg BID	60	4	6.67	3.22	2.07	0.35	12.98	0.0384
	Placebo -> 10 mg BID	60	3	5.00	2.81	1.78	-0.51	10.51	0.0756
MONTH 4(NRI)	CP-690,550 5 mg BID	241	48	19.92	2.57	7.74	14.87	24.96	<0.0001
	CP-690,550 10 mg BID	242	63	26.03	2.82	9.23	20.50	31.56	<0.0001
	Placebo -> 5 mg BID	60	8	13.33	4.39	3.04	4.73	21.93	0.0024
	Placebo -> 10 mg BID	60	9	15.00	4.61	3.25	5.96	24.04	0.0011
MONTH 5(NRI)	CP-690,550 5 mg BID	241	51	21.16	2.63	8.04	16.00	26.32	<0.0001
	CP-690,550 10 mg BID	242	69	28.51	2.90	9.82	22.82	34.20	<0.0001
	Placebo -> 5 mg BID	60	11	18.33	5.00	3.67	8.54	28.12	0.0002
	Placebo -> 10 mg BID	60	11	18.33	5.00	3.67	8.54	28.12	0.0002
MONTH 6(NRI)	CP-690,550 5 mg BID	241	53	21.99	2.67	8.24	16.76	27.22	<0.0001
	CP-690,550 10 mg BID	242	71	29.34	2.93	10.02	23.60	35.08	<0.0001
	Placebo -> 5 mg BID	60	12	20.00	5.16	3.87	9.88	30.12	0.0001
	Placebo -> 10 mg BID	60	13	21.67	5.32	4.07	11.24	32.09	<0.0001

<u>Study A3921044</u>: Phase 3 Randomized, Double Blind, Placebo Controlled Study of the Efficacy and Safety of 2 Doses of tofacitinib in Patients With Active Rheumatoid Arthritis on Background Methotrexate (1-Year Analysis).

Methods

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 tofacitinib in patients with active RA on background MTX. Seven hundred and fifty (750) patients were randomized in 4 treatment groups (tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo to tofacitinib 5 mg BID, placebo to tofacitinib 10 mg BID). 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 was ongoing. At month 3, the tender/painful and swollen joint counts were calculated and compared to the patient's individual Baseline values. If there was not a 20% improvement in both the tender/painful and swollen joint counts, the patient was considered a non-responder patient. If a non-responder patient was randomized to active treatment, he had to remain on the same treatment, at the same dose, for the duration of the study. If a non-responder patient was randomized to placebo, he switched to the second predetermined treatment

(either 5 mg or 10 mg tofacitinib) in a blinded manner for the remainder of the study. 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.

Study Participants

To be eligible in this study, patients were required to have active RA on background DMARDs, evidence of at least 3 distinct joint erosions on postero-anterior (PA) hand and wrist or antero-posterior (AP) foot radiographs (locally read) **OR** if radiographic evidence of joint erosion was not available, the patient must have had an RF, **OR** antibodies to anti-CCP+. Exclusion criteria were similar to other studies with regards the safety risks.

Treatments

Study medications were self-administered orally as 5 and 10 mg tablets BD. The background DMARD was specified to be MTX (supplemented with folic acid) which must have been dosed orally or parenterally for at least 4 months and the dose stable for at least 6 weeks before the first dose of study drug and then remained stable during the study. Concomitant therapy with stably dosed “low dose” oral glucocorticoids (≤10 mg/d prednisone equivalent), NSAIDs, and specified analgesics was allowed.

Objectives

Primary objectives

To be assessed in the following sequence:

- To compare the efficacy of tofacitinib in doses of 5 mg BID and 10 mg BID versus placebo for the treatment of signs and symptoms of RA in patients with active RA on a stable background of MTX, as measured ACR20 response rates at Month 6.

- To compare evidence of preservation of joint structure after administration of tofacitinib in doses of 5 mg BID or 10 mg BID versus placebo in patients with active RA on a stable background of MTX, as measured by changes from Baseline using the van der Heijde modified Sharp score at month 6.

- To compare physical function status of patients after administration of tofacitinib in doses of 5 mg BID or 10 mg BID versus placebo using the Health Assessment Questionnaire-Disability Index (HAQ-DI) at month 3 compared to Baseline in patients with active RA on a stable background of MTX.

- To compare the rate of achieving Disease Activity Score (DAS28)-4 Erythrocyte Sedimentation Rate (ESR) <2.6 after administration of tofacitinib in doses of 5 mg BID or 10 mg BID versus placebo at Month 6 in patients with active RA on a stable background of MTX.

- To evaluate the safety and tolerability of tofacitinib in doses of 5 mg BID and 10 mg BID

vs. placebo in patients with active RA on a stable background of MTX.

Outcomes/endpoints

Primary endpoints

- Signs and symptoms as measured by ACR 20 at Month 6;

- Structure preservation as measured by the total modified Sharp score (mTSS) change from baseline at Month 6;

- Physical function as measured by the HAQ-DI change from baseline at Month 3

- Incidence of DAS28-4 (ESR) <2.6 at Month 6.

Main secondary Efficacy Endpoints

Change from baseline in mTSS at Months 12 and 24; Erosion and JSN scores at months 6, 12 and 24; Rate of not progressing in mTSS (≤0.5 unit) at months 6, 12 and 24; Rate of no new erosions in Erosion score (≤0.5 unit) at months 6, 12 and 24; DAS28-3 (CRP) and DAS28-4(ESR) , that is, separate endpoints, analysed separately; Durability of ACR20, ACR50, ACR70, DAS28 response rates; SF-36; Actual and change from baseline in Work Limitations Questionnaire (WLQ); Actual and change from baseline in the EuroQol EQ-5D; Actual and change from baseline in the Medical Outcomes Study (MOS)-Sleep Scale; Actual and change from baseline in the FACIT Fatigue Scale; Rates of clinically meaningful decrease in the HAQ-DI.

Sample size

The endpoint that determined the sample size for this trial was the preservation of joint structure as measured by mTSS. 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. For the ACR20 analysis, the first endpoint which was to be analyzed in the stepdown approach, this sample size yielded over 90% power assuming a difference in response rates of at least 20% (with the placebo response at 30%).For the analysis of the mTSS, power was planned to be approximately 90%.For the analysis of the HAQ-DI, the third endpoint in the stepdown approach, the sample size resulted in over 90% power for differences of 0.3 or greater, assuming SD of 0.75. For the analysis of DAS28-4(ESR) <2.6, this sample size resulted in 99% power for differences in response rates of at least 15% (with placebo response at 10%).

Randomisation

At the study site, randomization of patients was accomplished using an interactive voice response system (IVRS), an automated web/telephone randomization system provided by the sponsor. Seven hundred and fifty (750) patients were randomized in a 4:4:1:1 ratio to 1 of the 4 parallel treatment sequences.

Blinding (masking)

This study was patient, investigator and Sponsor-blinded.

Statistical methods

This protocol was designed to address objectives based on 4 primary endpoints. In order to preserve Type I error, each objective was assessed sequentially using a gate-keeping or stepdown approach where statistical significance can be claimed for a given endpoint only if the prior endpoint in the sequence met the requirement for significance. Additionally, as there were 2 doses within each endpoint, the gate-keeping or stepdown approach was also applied, ie, the high dose (10 mg BID) at a given endpoint could achieve significance only if the high dose at the prior endpoint was significant; the low dose (5 mg BID) at a given endpoint could achieve significance only if both the high dose at the same endpoint and the low dose at the prior endpoint were significant. The FAS was the primary analysis population for this study. Data from patients at Sites 1048 and 1174 were excluded from the FAS. For mTSS, patients who were advanced at Month 3 had their Month 6 measurement calculated using a linear extrapolation from the X-rays taken at Baseline and Month 3. For Month 12, comparisons to placebo were done by linearly extrapolating a Month 12 value based on Baseline and Month 6. All Sharp Score-related variables were imputed using this method. Binary variables (rates of patients with no progression in mTSS and rates of patients with no progression in mean erosion score) were analyzed using normal approximation to the binomial.

Results

Participant flow

Table 53

Table 7. Patient Disposition Through Month 12 by Treatment Sequence (1-Year Analysis)

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Screened: 1291				
Assigned to Study Treatment	321	319	81	79
Treated	321	316	81	79
Ongoing at Date of Cutoff[a]	250 (77.9)	265 (83.1)	64 (79.0)	64 (81.0)
Discontinued	71 (22.1)	51 (16.0)	17 (21.0)	15 (19.0)
Patient Died[b]	1 (0.3)	1 (0.3)	0	0
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)
Study terminated by Sponsor[c]	1 (0.3)	0	2 (2.5)	1 (1.3)
Not Related to Study Drug	35 (10.9)	28 (8.8)	7 (8.6)	9 (11.4)
Adverse event	9 (2.8)	7 (2.2)	0	2 (2.5)
Lost to follow-up	5 (1.6)	0	0	3 (3.8)
Protocol violation	6 (1.9)	6 (1.9)	3 (3.7)	1 (1.3)
Pregnancy	1 (0.3)	1 (0.3)	0	0
Site closure[d]	1 (0.3)	0	0	1 (1.3)
Patient no longer willing to participate in study	8 (2.5)	11 (3.5)	2 (2.5)	2 (2.5)
Other	1 (0.3)[e]	1 (0.3)[f]	2 (2.5)[g]	0
Other: Patient moving	4 (1.2)	1 (0.3)	0	0
Other: Sponsor request	0	1 (0.3)	0	0

Recruitment

First Subject First Visit: 31 March 2009
Last Subject Last Visit: 01 April 2011

Conduct of the study

Table 54 A3921044 Protocol Deviation Summary Table

	Placebo/ CP-690,550 5 mg BID	Placebo/ CP-690,550 10 mg BID	CP-690,550 5 mg BID/ CP-690,550 5 mg BID	CP-690,550 10 mg BID/ CP-690,550 10 mg BID	Screen Failure	Total
Concomitant Medication*	5	3	29	26	5	**68**
Inclusion/Exclusion Criteria	6	4	32	25	9	**76**
Informed Consent	6	7	27	35	32	**107**
Investigational Product**	3	2	14	15	0	**34**
Laboratory	24	17	80	68	140	**329**
Other	0	1	4	1	3	**9**
Procedures/Tests	21	15	70	68	52	**226**
Protocol Specific Discontinuation Criteria	1	0	5	8	0	**14**
Randomization	0	0	2	4	0	**6**
Safety Reporting	1	0	0	1	0	**2**
Visit Schedule	0	1	10	1	2	**14**
Grand Total	**67**	**50**	**273**	**252**	**243**	**885**

**Concomitant medications include prohibited medications and rescue errors affecting the efficacy of primary endpoints before month 6.*
*** Investigational product includes advancement errors and interrupting study medication before month 6.*
Source: Appendix 2: Table 16.2.2a Protocol Deviations with Drug Assignment for A3921044
Abbreviations: BID=twice a day, mg=milligram,

Baseline data

Table 55 Baseline Characteristics by Treatment Sequence (1-Year Analysis)

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Baseline Characteristic Parameter	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Disease duration (rheumatoid arthritis) (duration since first diagnosis, years):				
N	321	316	81	79
Mean	8.9	9.0	8.8	9.5
Range	0.3 – 43.0	0.3 – 42.0	0.6 – 30.8	0.4 – 43.5
Rheumatoid factor, n (%):				
N	315	308	79	77
Negative	78 (24.8)	69 (22.4)	16 (20.3)	19 (24.7)
Positive	237 (75.2)	239 (77.6)	63 (79.7)	58 (75.3)
Anti-CCP antibodies, n (%):				
N	320	315	81	79
Negative (<20 units)	45 (14.06)	49 (15.56)	13 (16.05)	14 (17.72)
Weak positive (20-39 units)	21 (6.56)	19 (6.03)	8 (9.88)	1 (1.27)
Moderate positive (40-59 units)	16 (5.0)	12 (3.81)	3 (3.70)	5 (6.33)
Strong positive (≥60 units)	238 (74.38)	235 (74.60)	57 (70.37)	59 (74.68)
DAS28-3(CRP):				
N	316	309	79	77
Mean (SD)	5.22 (0.88)	5.20 (0.87)	5.14 (0.89)	5.18 (0.86)
Range	2.86 – 7.55	2.92 – 7.93	3.27 – 6.70	3.22 – 7.17
DAS28-4(ESR):				
N	316	307	78	76
Mean (SD)	6.35 (0.90)	6.28 (0.94)	6.25 (0.95)	6.32 (0.97)
Range	2.84 – 8.67	3.79 – 8.69	4.12 – 8.42	4.27 – 8.56
Sharp Scores (mTSS):				
N	286	295	71	68
Mean (SD)	31.1 (47.71)	37.3 (54.10)	35.0 (43.20)	30.1 (40.45)
Range	0.0 – 337.0	0.0 – 311.5	0.0 – 170.5	0.0 – 208.5
HAQ-DI:				
N	315	309	79	77
Mean (SD)	1.41 (0.68)	1.39 (0.66)	1.40 (0.62)	1.23 (0.73)
Range	0.00 – 3.00	0.00 – 2.88	0.00 – 2.88	0.00 – 2.88

Source: Tables 14.1.2.1.3, 14.1.2.1.4, 14.1.2.2, 14.2.11.2, 14.2.12.2, 14.2.13.2, and 14.2.15.1.1
Abbreviations: BID=twice daily, CCP=cyclic citrullinated peptide, DAS=Disease Activity Score, HAQ-DI=Health Assessment Questionnaire - Disability Index, SD=standard deviation, N=number of patients, n=number of patients meeting prespecified criteria, mTSS=Modified Total Sharp Score, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate
CP-690,550 5 mg BID or CP-690,550 10 mg BID patients received this dose from Day 1; Placebo patients received this dose from Day 1 to either Month 3 or Month 6; Placebo → 5 mg BID or Placebo → 10 mg BID patients received Placebo from Day 1 to either Month 3 or Month 6 then changed to either CP-690,550 5 mg BID or CP-690,550 10 mg BID.
mTSS (Sharp/van der Heijde method) defined in Section 9.5.3.1.

Table 56 Baseline Characteristics by Treatment Sequence (1-Year Analysis)

Page 2 of 2

Baseline Characteristic Parameter	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Tender joint counts:				
N	316	309	79	77
Mean (SD)	24.1 (14.01)	23.0 (14.52)	23.3 (13.48)	22.6 (12.87)
Range	6.0 – 68.00	6.0 – 68.00	6.0 – 68.00	6.0 – 58.00
Swollen joint counts:				
N	316	309	79	77
Mean (SD)	14.1 (8.21)	14.4 (7.74)	14.0 (7.90)	14.5 (8.89)
Range	6.0 – 58.00	6.0 – 47.00	6.0 – 45.00	6.0 – 55.00
ESR (mm/Hr):				
N	316	307	78	76
Mean (SD)	50.1 (24.48)	50.5 (26.99)	47.8 (22.14)	54.4 (26.94)
Range	3.0 – 135.00	3.0 – 140.00	12.0 – 115.00	12.0 – 126.00
CRP (mg/L):				
N	316	309	79	77
Mean (SD)	15.5 (19.07)	17.0 (26.93)	12.2 (14.54)	15.3 (15.05)
Range	0.2 – 174.00	0.2 – 360.00	0.2 – 94.50	0.4 – 77.50

Source: Tables 14.2.4.1, 14.2.5.2, 14.2.6.2, 14.2.7.2
Abbreviations: BID=twice daily, CRP=C-reactive protein, ESR=erythrocyte sedimentation rate, SD=standard deviation, Hr=hour, N=number of patients, mm/hr=millimeters/hour
CP-690,550 5 mg BID or CP-690,550 10 mg BID patients received this dose from Day 1; Placebo patients received this dose from Day 1 to either Month 3 or Month 6; Placebo → 5 mg BID or Placebo → 10 mg BID patients received Placebo from Day 1 to either Month 3 or Month 6 then changed to either CP-690,550 5 mg BID or CP-690,550 10 mg BID.

Numbers analysed

Table 57

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Assigned to Study Treatment	321	319	81	79
Treated	321	316[a]	81	79
Completed	0	0	0	0
Discontinued	71 (22.1)	51 (16.0)	17 (21.0)	15 (19.0)
Ongoing at date of cut-off[b]	250 (77.9)	265 (83.1)	64 (79.0)	64 (81.0)
Analyzed for Efficacy				
Full Analysis Set[c]	316 (98.4)	309 (96.9)	79 (97.5)	77 (97.5)
Per Protocol Analysis Set	299 (93.1)	286 (89.7)	75 (92.6)	76 (96.2)
Analyzed for Safety				
Adverse events	321 (100.0)	316 (99.1)	81 (100.0)	78 (98.7)
Laboratory data	318 (99.1)	315 (98.7)	81 (100.0)	78 (98.7)

Outcomes and estimation

Primary endpoints

ACR 20 responses rate at month 6

Table 58 Normal Approximation to ACR20 Response Rates at Month 6 (FAS, NRI, Differences From Placebo, 1-Year Analysis)

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

Source: Table 14.2.1.1

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

Modified Total Sharp Scores (mTSS) at month 6

Table 59. Statistical Analysis of Change from Baseline in Modified Total Sharp Scores at Months 6 Comparison to Placebo Using Nonlongitudinal Linear Mixed Model (FAS, Imputation Using Linear Extrapolation) – Study A3921044

Treatment	N	LS Means	Comparison to Placebo			
			Difference	95% CI for Difference		P- Value
				Lower	Upper	
Month 6						
tofacitinib 5 mg BID	277	0.12	-0.34	-0.73	0.04	0.0792
tofacitinib 10 mg BID	290	0.06	-0.40	-0.79	-0.02	0.0376
Placebo	139	0.47	Not applicable			

Patients in the placebo group received placebo from Day 1 to either Month 3 or Month 6, and received tofacitinib 5 mg or 10 mg BID based on their randomized sequence after Month 3 or 6.

Change From Baseline in HAQ-DI at Month 3 (1-Year Analysis)

Table 60 Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, Differences From Placebo, 1-Year Analysis)

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

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

Rates of Patients (%) Achieving DAS28-4(ESR) <2.6 at Month 6

Table 61 Summary (%) of Patients Achieving DAS28-4(ESR) <2.6 at Month 6 (FAS, No Imputation, Comparisons to Placebo, 1-Year Analysis)

Treatment	N	n	%	Comparison to Placebo			
				Difference	95% CI for Difference		p-value
					Lower	Upper	
CP-690,550 5 mg BID	265	19	7.17	5.61	1.85	9.38	0.0034
CP-690,550 10 mg BID	257	47	18.29	16.73	11.55	21.92	<0.0001
Placebo	129	2	1.55				

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

Main secondary endpoints

Secondary endpoints on structural damage

Table 62. Proportions of Patients (%) with No Radiographic Progression (mTSS Change ≤ 0.5) at Months 6 and 12 (FAS, LEP, Comparisons to Placebo, 1-Year Analysis) – Study A3921044

Time point / Treatment	N	n	%	Difference From Placebo			
				Difference in %	95% CI for Difference		p-value
					Lower	Upper	
Month 6							
tofacitinib 5 mg BID	277	246	88.81	11.11	3.25	18.96	0.0055
tofacitinib 10 mg BID	290	252	86.9	9.19	1.26	17.13	0.0230
Placebo	139	108	77.7				
Month 12							
tofacitinib 5 mg BID	286	246	86.01	11.91	3.59	20.23	0.0050
tofacitinib 10 mg BID	295	255	86.44	12.33	4.07	20.6	0.0034
Placebo	139	103	74.1				

BID=twice daily, CI=confidence interval, FAS=full analysis set, N=number of patients, n=number of patients meeting prespecified criteria, LEP=linear extrapolation
No progression defined as ≤ 0.5units in mTSS

Table 63. Proportions of Patients (%) with No Progression in Erosion Score (≤ 0.5 Unit Change) at Months 6 and 12 (FAS, LEP, Comparisons to Placebo, 1-Year Analysis) – Study A3921044

Time point/ Treatment	N	n	%	Difference From Placebo			
				Difference in %	95% CI for Difference		p-value
					Lower	Upper	
Month 6							
tofacitinib 5 mg BID	277	260	93.86	6.09	-0.04	12.22	0.0516
tofacitinib 10 mg BID	290	271	93.45	5.67	-0.46	11.82	0.0701
Placebo	139	122	87.77				
Month 12							
tofacitinib 5 mg BID	286	263	91.96	8.50	1.56	15.44	0.0162
tofacitinib 10 mg BID	295	275	93.22	9.76	2.95	16.57	0.0049
Placebo	139	116	83.45				

BID=twice daily, CI=confidence interval, FAS=full analysis set, N=number of patients, n=number of patients meeting prespecified criteria, LEP=linear extrapolation
No progression in erosion score defined as ≤ 0.5 units change in erosion score

Study A3921032: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of tofacitinib in Patients With Active Rheumatoid Arthritis on Background Methotrexate With Inadequate Response to TNF Inhibitors

Methods

This randomized, placebo-controlled study of 6 month duration evaluated efficacy and safety of 5 and 10 mg doses of tofacitinib, in association with methotrexate, in the treatment of patients with active RA previously in failure and/or intolerant to biologic anti-TNF alpha inhibitors. Three hundred and nighty-nine (399) patients were randomized to receive four treatment groups (tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo to tofacitinib 5 mg BID, placebo to tofacitinib 10 mg BID). Following 3 months of treatment, patients who were randomized to a sequence that first administered placebo began receiving tofacitinib in a blinded manner at either 5 mg or 10 mg for the remainder of the 6-month study.

Study Participants

To be eligible for participation, patients were required to have active RA, ongoing treatment with an adequate and stable dose of MTX, at least 1 approved TNF-inhibiting biologic agent inadequately effective and/or not tolerated according to the opinion of the investigator.

Treatments

Study medications were self-administered orally as 5 and 10 mg tablets BD. The background DMARD was specified to be MTX (supplemented with folic acid) which must have been dosed orally or parenterally for at least 4 months and the dose stable for at least 6 weeks before the first dose of study drug and then remained stable during the study. Concomitant therapy with stably dosed “low dose” oral glucocorticoids (≤10 mg/d prednisone equivalent), NSAIDs, and specified analgesics was allowed.

Objectives

Primary objectives

- To compare the efficacy of tofacitinib, in doses of 5 mg twice daily (BID) and 10 mg BID, vs. placebo for the treatment of signs and symptoms of RA, in patients with RA on background MTX who had an inadequate response to a TNF inhibitor, as measured by ACR20 response rates at Month 3.
- To compare physical function status of patients as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI) response at Month 3.

- To compare the rate of achieving Disease Activity Score (DAS) 28-4 (erythrocyte sedimentation rate [ESR]) <2.6 at Month 3.
- To compare the safety and tolerability of tofacitinib, in doses of 5 mg BID and 10 mg BID, vs. placebo.

Secondary objectives

- To compare the efficacy of tofacitinib, in doses of 5 mg BID and 10 mg BID, vs. placebo for the treatment of signs and symptoms of RA in patients with RA on background MTX who had an inadequate response to a TNF inhibitor at all other time points as measured by ACR20, ACR 50, ACR70, and DAS28 response rates.
- To compare the incidence of DAS28 <2.6 and DAS28 ≤ 3.2 at each visit.
- To compare effects on all health outcomes measures in the study at each visit, as appropriate for the specific outcome, compared to baseline.

Outcomes/endpoints

Primary endpoints

- ACR20 responses at month 3
- Physical function as measured by the HAQ-DI at month 3
- Improved disease activity as measured by DAS28-4(ESR) <2.6 at month 3

Secondary endpoints included: signs and symptoms of RA, as measured by ACR20 responder rates vs. placebo analysed at all time points other than Month 3; ACR50 and ACR70 responder rates at all time points; and incidence and response rates of DAS28-3(CRP) and DAS28-4(ESR).

Sample size

To preserve Type I error, a step-down procedure was used. Thus determination of sample size is driven by sample-size calculations made separately for each endpoint. 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; and

- 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

At the study site, randomization of patients was accomplished using an interactive voice response system (IVRS), an automated web/telephone randomization system provided by the sponsor.

Three hundred and ninety-nine (399) patients were randomized in a 2:2:1:1 ratio to one of the four parallel treatment sequences. Following 3 months of treatment, patients who were randomized to a sequence that first administered placebo began receiving tofacitinib in a blinded manner at either 5 mg or 10 mg for the remainder of the 6-month study.

Blinding (masking)

This study was patient, investigator and Sponsor-blinded.

Statistical methods

This study protocol was designed to address objectives based on 3 primary endpoints. In order to preserve Type I error, each objective was assessed sequentially using gate-keeping or step-down approach where statistical significance can be claimed for a given endpoint only if the prior endpoint in the sequence met the requirement for significance. Additionally, as there were 2 doses within each endpoint, the gate-keeping or step-down approach was also applied, i.e., the high dose (10 mg BID) at a given endpoint could achieve significance only if the high dose at prior endpoint was significant; the low dose (5 mg BID) at a given endpoint could achieve significance only if both the high dose at the same endpoint and the low dose at the prior endpoint were significant. For each endpoint and for each dose group, the comparison with placebo was conducted using a significance level (alpha) set at 0.05 (2-sided) or equivalently 0.025 (1-sided).

Results

Participant flow

Table 64 Patient Disposition

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Screened: 589				
Assigned to Study Treatment	133	134	66	66
Treated	133	134	66	66
Completed	107 (80.5)	103 (76.9)	53 (80.3)	48 (72.7)
Discontinued	26 (19.5)	31 (23.1)	13 (19.7)	18 (27.3)
Patient Died	0	0	0	1 (1.5)
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)
Not Related to Study Drug	16 (12.0)	19 (14.2)	7 (10.6)	9 (13.6)
Adverse event	4 (3.0)	5 (3.7)	1 (1.5)	4 (6.1)
Other	1 (0.8)	1 (0.7)	1 (1.5)	0
Protocol violation	2 (1.5)	8 (6.0)	3 (4.5)	4 (6.1)
Patient no longer willing to participate in study	9 (6.8)	5 (3.7)	2 (3.0)	1 (1.5)

Source: Tables 14.1.1.1, 14.1.1.3, 16.2.1.1, 16.2.1.2, and 16.2.7
Information related to study discontinuations from Table 14.1.1.3 is from the patient summary page of the Case Report Form.
Abbreviations: BID = twice daily, No. = number

Recruitment

First Subject First Visit: 12 October 2009
Last Subject Last Visit: 17 March 2011

Conduct of the Study

Table 65 A3921032 Protocol Deviation Summary Table

	Placebo/ CP-690,550 5 mg BID	Placebo/ CP-690,550 10 mg BID	CP-690,550 5 mg BID/ CP-690,550 5 mg BID	CP-690,550 10 mg BID/ CP-690,550 10 mg BID	Screen Failure	Total
Concomitant Medication	7	5	9	14	1	**36**
Inclusion/Exclusion Criteria	1	5	2	10	6	**24**
Informed Consent	5	13	18	14	18	**68**
Investigational Product	18	10	27	39	1	**95**
Laboratory	14	22	34	33	6	**109**
Other	0	0	0	0	0	**0**
Procedures/Tests	20	20	44	40	3	**127**
Protocol Specific Discontinuation Criteria	0	0	1	0	0	**1**
Randomization	0	0	1	0	0	**1**
Safety Reporting	2	0	1	0	0	**3**
Visit Schedule	5	9	9	13	0	**36**
Grand Total	**72**	**84**	**146**	**163**	**35**	**500**

**Concomitant medications include prohibited medications and rescue errors affecting the efficacy of primary endpoints before month 3.*
*** Investigational product includes advancement errors and interrupting study medication before month 3.*
Source: Appendix 5 Table 16.2.2a Protocol Deviations with Drug Assignment for A3921032
Abbreviations: BID=twice a day, mg=milligram,

Baseline data

Table 66 Baseline Characteristics

Baseline Characteristic Parameter	CP-690,550 5 mg BID N=133	CP-690,550 10 mg BID N=134	Placebo → CP-690,550 5 mg BID N=66	Placebo → CP-690,550 10 mg BID N=66
Disease duration (rheumatoid arthritis) (duration since first diagnoses, years):				
Mean	13.0	12.6	11.3	11.2
Range	1.2-55.0	0.7-42.0	1.3-47.0	0.4-36.0
Rheumatoid factor:				
Negative	39.39	38.06	39.39	29.23
Positive	60.61	61.94	60.61	70.77
Anti-CCP:				
Negative	31.54	30.23	26.15	22.22
Positive	68.46	69.77	73.85	77.78
DAS28-3(CRP):				
Mean (SD)	5.38 (1.00)	5.31 (0.90)	5.23 (0.93)	5.55 (0.96)
Range	2.63-7.65	2.59-7.48	3.44-7.42	2.90-7.43
DAS28-4(ESR):				
Mean (SD)	6.48 (1.03)	6.40 (0.89)	6.29 (0.89)	6.64 (1.03)
Range	3.69-8.92	4.20-8.49	4.02-8.34	3.25-8.94
HAQ-DI:				
Mean (SD)	1.60 (0.66)	1.50 (0.61)	1.59 (0.62)	1.66 (0.69)
Range	0-3.0	0-3.0	0-2.8	0-2.9
Tender joint counts:				
Mean (SD)	28.40 (18.29)	27.55 (15.70)	26.68 (16.38)	29.70 (17.08)
Range	6.0-68.0	6.0-66.0	6.0-68.0	7.0-68.0
Swollen joint counts:				
Mean (SD)	16.20 (10.06)	16.57 (9.87)	15.05 (8.98)	19.29 (11.84)
Range	5.0-62.0	6.0-60.0	5.0-58.0	6.0-62.0
ESR (mm/Hr):				
Mean (SD)	47.83 (26.08)	45.16 (22.88)	43.74 (23.76)	49.66 (25.28)
Range	5.0-130.0	10.0-126.0	5.0-119.0	7.0-120.0
CRP (mg/L):				
Mean (SD)	19.33 (27.50)	15.73 (21.59)	15.40 (15.87)	17.98 (22.78)
Range	0.2-142.0	0.2-109.0	0.6-79.2	0.6-116.0

Concomitant medication at baseline

Table 67 DMARDs Taken Prior to Screening

Parameter	CP-690,550 5 mg BID N=133 n	CP-690,550 10 mg BID N=134 n	Placebo → CP-690,550 5 mg BID N=66 n	Placebo → CP-690,550 10 mg BID N=66 n
Patients taking methotrexate prior to screening				
Methotrexate, n (%)*	117 (88.0)*	127 (94.8)	58 (87.9)	56 (84.8)
Methotrexate sodium, n (%)	14 (10.5)	7 (5.2)	8 (12.1)	10 (15.2)
Patients taking DMARDS other than methotrexate prior to screening				
No. (%) patients with any drug treatment	53 (39.8)	37 (27.6)	16 (24.2)	17 (25.8)
Auranofin	1	2	0	1
Aurothioglucose	0	1	0	1
Chloroquine	3	1	0	1
Chloroquine phosphate	2	5	3	0
Gold	2	3	0	1
Gold preparations	2	4	0	0
Hydroxychloroquine	7	3	3	4
Hydroxychloroquine phosphate	7	5	2	3
Hydroxychloroquine sulfate	2	2	2	1
Leflunomide	26	21	12	11
Mesalazine	0	1	0	0
Minocycline	0	0	0	1
Penicillamine	1	1	0	0
Sodium aurothiomalate	2	1	1	2
Sulfasalazine	18	13	3	8
Patients taking other biologic DMARDs prior to screening				
No. (%) of patients with any drug treatment	21 (15.8)	11 (8.2)	4 (6.1)	10 (15.2)
Abatacept	15	8	3	8
Anakinra	0	0	0	1
Canakinumab	1	0	0	0
Rituximab	6	2	0	2
Tocilizumab	5	4	1	2

Source: Tables 14.4.2.2.1, 14.4.2.2.3, and 14.4.2.2.4
World Health Organization Drug (Version 02Q2) coding dictionary applied.
Patients may have received more than 1 treatment.
Abbreviations: DMARD = disease-modifying antirheumatic drug, BID = twice daily, N = number of patients, n = number of patients meeting prespecified criteria, No. = number
* Two additional patients not included in this table (10311009 and 10561009 [both assigned to CP-690,550 5 mg treatment sequence]) were on methotrexate before screening; this information was erroneously not entered into the database.

Table 68 TNF Inhibitors Taken Prior to Screening

Parameters	CP-690,550 5 mg BID n	CP-690,550 10 mg BID n	Placebo → CP-690,550 5 mg BID n	Placebo → CP-690,550 10 mg BID n
No. of patients	133	134	66	66
No. (%) of patients with any drug treatment	132 (99.2)	132 (98.5)	66 (100.0)	66 (100.0)
Adalimumab	65	74	36	42
Certolizumab	2	2	3	2
Certolizumab pegol	7	7	4	2
Etanercept	65	57	29	28
Golimumab	5	8	2	5
Infliximab	56	42	27	16

Table 69 Number of Previous TNF Inhibitors

Number of Previous TNF Inhibitors	Placebo N	CP-690,550 5 mg BID N	CP-690,550 10 mg BID N
One N = 257 (65%)	85	83	89
Two N = 106 (27%)	37	37	30
Three or more N = 32 (8%)	9	11	12

Source: Table a1.12

Numbers analysed

Table 70

No. (%) of Patients	CP-690,550 5 mg BID n (%)	CP-690,550 10 mg BID n (%)	Placebo → CP-690,550 5 mg BID n (%)	Placebo → CP-690,550 10 mg BID n (%)
Assigned to Study Treatment	133	134	66	66
Treated	133	134	66	66
Completed	107 (80.5)	103 (76.9)	53 (80.3)	48 (72.7)
Discontinued[a]	26 (19.5)	31 (23.1)	13 (19.7)	18 (27.3)
Analyzed for Efficacy:				
Full Analysis Set	133 (100.0)	134 (100.0)	66 (100.0)	66 (100.0)
Per Protocol Analysis Set[b]	127 (95.5)	123 (91.8)	61 (92.4)	63 (95.5)
Analyzed for Safety:				
Adverse events	133 (100.0)	134 (100.0)	66 (100.0)	66 (100.0)
Laboratory data	132 (99.2)	133 (99.3)	66 (100.0)	65 (98.5)

Outcomes and estimation

ACR 20 response rates at month 3

Table 71 Normal Approximation to ACR20 Response Rates at Month 3 (FAS, NRI, Difference From Placebo)

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

Source: Table 14.2.3.1.1
Abbreviations: ACR20 = American College of Rheumatology's (ACR) definition for calculating improvement in rheumatoid arthritis; calculated as a ≥20% improvement in tender and swollen joint counts and ≥20% improvement in 3 of the 5 remaining ACR core set measures, BID = twice daily, CI = confidence interval, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, NRI = nonresponder imputation

Changes From Baseline in HAQ-DI at Month 3

Table 72 Summary of LS Mean Changes From Baseline in HAQ-DI at Month 3 (FAS, NRI, Differences From Placebo)

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

Source: Table 14.2.13.3.1
Abbreviations: BID = twice daily, CI = confidence interval, FAS = full analysis set, HAQ-DI = Health Assessment Questionnaire - Disability Index, LS mean = least squares mean, N = number of patients, NRI = nonresponder imputation

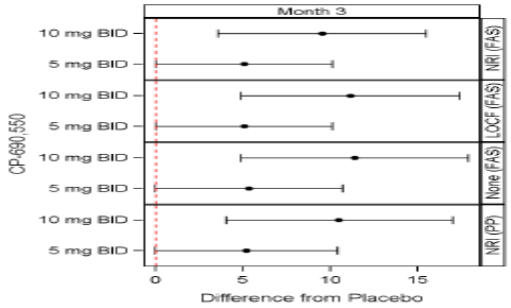
Rate of Patients Achieving DAS28-4(ESR) <2.6 Versus Placebo at Month 3

Table 73 Summary of Patients Achieving DAS28-4(ESR) <2.6 at Month 3 (FAS, NRI, Comparisons to Placebo)

Treatment	N	n	%	Comparison to Placebo			
				Difference	95% CI for Difference		P-value
					Lower	Upper	
CP-690,550 5 mg BID	119	8	6.72	5.05	0.00	10.10	0.0496
CP-690,550 10 mg BID	125	14	11.20	9.53	3.54	15.51	0.0017
Placebo	120	2	1.67				

Source: Table 14.2.15.10.1
Abbreviations: BID = twice daily, CI = confidence interval, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, NRI = nonresponder imputation

Figure 3 **Differences From Placebo in Response Rates (%) and 95% Confidence Intervals for DAS28-4(ESR) <2.6**



Source: Tables 14.2.15.10.1, 14.2.15.10.5, 14.2.15.11.1, 14.2.15.12.1 (DAS28-4(ESR) < 2.6 Response)

None = no imputation
Abbreviations: BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, NRI = nonresponder imputation, LOCF = last observation carried forward, PP = per protocol

Main secondary endpoints

At month 6, ACR20 response rates for patients in the tofacitinib 5 mg and 10 mg were 51.5% and 54.9%, respectively, compared with 45.5% and 40.0% for patients in the placebo → tofacitinib 5 mg and placebo → tofacitinib 10 mg groups, respectively.

At month 6, ACR50 response rates for patients in the tofacitinib 5 mg and 10 mg groups were 37.12% and 30.08%, respectively, compared with 28.79% and 20.0% for patients in the placebo → tofacitinib 5 mg and placebo → tofacitinib 10 mg dose mg groups, respectively.

At month 6, ACR70 response rates for patients in the tofacitinib 5 mg and 10 mg groups were 15.91% and 15.79%, respectively, compared with 10.61% and 9.23% for patients in the placebo → tofacitinib 5 mg and placebo →tofacitinib 10 mg groups, respectively.

Subgroups analyses by number of previous TNF inhibitors

Additional analyses were conducted to determine if the efficacy of tofacitinib was affected by either the number of previous TNF inhibitors or by the reason for discontinuing prior TNF inhibitors. The ACR20 response rates, are summarised below.

Table 74 **ACR20 Response Rate by Number of Previous TNF Inhibitors**

Number of Previous TNF Inhibitors	Placebo	CP-690,550 5 mg BID	CP-690,550 10 mg BID
ACR20 Response Rate at Month 3			
One N=257/399 (64.4%)	30.59%	43.37%	48.31%§
Two N=104/399 (26.0%)	10.81%	37.84%§	53.33%‡
Three or more N=32/399 (8.0%)	22.22%	36.36%	41.67%

§p<0.05 vs placebo at 3 months (unadjusted)
‡ p<0.0001 vs placebo at 3 months (unadjusted)
Source: Table a1.12
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, N = number of patients, TNF = tumor necrosis factor

Table 75. ACR Response Rate by Reason for Inadequate Response to Prior TNF inhibitors

Reason for Inadequate Response to Prior TNF inhibitors	Placebo	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
ACR20 Response Rate at Month 3			
Adverse event (AE) N=55/399 (13.8%)	21.05%	23.53%	57.89%§
Lack of efficacy N=260/399 **(65.2%)**	26.51%	40.66%§	46.51%§
Lack of efficacy and AE N=78/399 (19.5%)	20.69%	56.52%§	50.00%§

Study A3921046: Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of 2 Doses of tofacitinib in Patients with Active Rheumatoid Arthritis on Background DMARDs

Methods

Study 1046 was a phase 3 randomized, one year, double-blind, placebo-controlled, parallel group study to compare tofacitinib 5 mg and 10 mg BID versus placebo, on background DMARDs, in the treatment of patients with active RA who have had an inadequate response to at least one DMARDs (traditional or biologic).

Study Participants

To be eligible, patients have to remain on at least 1 background traditional DMARD. Before screening, 84.3% patients had taken MTX, only 6.6% had taken anti-TNF inhibitors and 2.9% patients had taken other biologic DMARDs. Therefore, included patients were not in failure of biologic DMARDS. Moreover, albeit inclusion criteria required all patients to be on background DMARDs, it seems that only 66 to 73% patients were treated concomitantly with a single DMARD.

Treatments

Study medications were self-administered orally as 5 and 10 mg tablets BD. The background DMARD was traditional small molecules that are not potent immunosuppressive agents, including MTX, leflunomide, sulfasalazine, gold salts, penicillamine, antimalarials and combinations thereof.

Objectives

Primary objectives

- To compare the efficacy of tofacitinib in doses of 5 mg BID and 10 mg BID versus placebo for the treatment of signs and symptoms of RA in patients with active RA who have had an inadequate response to a DMARD (traditional or biologic), as measured by (ACR20) response rates at Month 6.
- To compare physical function status of patients after administration of tofacitinib in doses of 5 mg BID or 10 mg BID versus placebo using HAQ-DI at Month 3 compared to baseline in patients with active RA on background traditional DMARDs.
- To compare the rate of achieving disease activity score (DAS) 28-4 ([ESR]) <2.6 at month 6 in patients with active RA after administration of tofacitinib, in doses of 5 mg BID and 10 mg BID versus placebo.

- To evaluate the safety and tolerability of tofacitinib in doses of 5 mg BID and 10 mg BID versus placebo in patients with active RA on background traditional DMARDs.

Outcomes/endpoints

Primary endpoints

- Signs and symptoms as measured by ACR 20 at Month 6
- Physical function as measured by the HAQ-DI change from baseline at Month 3
- Incidence of DAS28-4 (ESR) <2.6 at Month 6

Secondary endpoints included: ACR20 Responder rates at times other than Month 6; ACR50 Responder rates; ACR70 Responder rates; Actual and change from baseline of the 7 individual components (tender joint count, swollen joint count, patient assessment of arthritis pain, physician global assessment of arthritis, patient global assessment of arthritis, CRP, and HAQ-DI) of the ACR criteria variables (separate analyses); Actual and change from baseline in DAS28 which included the following DAS: DAS28-3(CRP), and DAS28-4(ESR), that is, separate endpoints, analysed separately; Incidences of DAS28-3 (CRP) <3.2, and DAS28-4(ESR) <3.2 (separate endpoints, analysed separately); Incidences of DAS28-4(ESR) <2.6 at time points other than Month 6; Incidences of DAS28-3(CRP) <2.6; DAS 28 response rates (No improvement vs. improvement ([Moderate improvement or Good improvement]), based on DAS28-3(CRP) and DAS28-4(ESR), (separate endpoints, analysed separately); ACR70 Response for at least 6 Months; Durability of ACR20, ACR50, ACR70, DAS28 response rates: Actual and change from baseline in the SF-36 8 domain scores and 2 component scores (separate analyses); Actual and change from baseline in Work Limitations Questionnaire (WLQ) 4 domain scores and the work loss index (separate analyses); Actual and change from baseline in the EuroQoL EQ-5D.

Sample size

This protocol was designed to address objectives based on 3 primary endpoints. In order to preserve Type I error in the primary analyses, each primary efficacy endpoint was assessed sequentially using gate-keeping or step-down approach where statistical significance can be claimed for a given endpoint only if the prior endpoint in the sequence met the requirement for significance. Additionally, as there were 2 dose levels to be evaluated within each endpoint, the gate-keeping or step-down approach was also applied, i.e., the high dose (10 mg BID) at a given endpoint could achieve significance only if the high dose at the prior endpoint was significant; the low dose (5 mg BID) at a given endpoint could achieve significance only if both the high dose at the same endpoint and the low dose at the prior endpoint were significant.

For each endpoint, and for each dose group, the comparison with placebo was conducted using a significance level (alpha) set at 0.05 (2-sided) or equivalently 0.025 (1-sided).

For the ACR20 analysis, the first endpoint which was to be analysed in the step-down approach, this sample size yielded over 90% power assuming a difference in response rates of at least 20% (with the placebo response at 30%).

For the analysis of the HAQ-DI, the second endpoint in the step-down approach, the sample size resulted in over 90% power (97%) for differences of 0.3 or greater, assuming a standard deviation (SD) of 0.75. For the analysis of DAS28-4(ESR) <2.6, this sample size resulted in over 90% power (99%) for differences in response rates of at least 15% (with placebo response at 10%).

Randomisation

At the study site, randomization of patients was accomplished using an interactive voice response system (IVRS), an automated web/telephone randomization system provided by the sponsor.

Seven hundred and ninety-five patients (795) patients were randomized in a 4:4:1:1 ratio to one of the following four parallel treatment sequences: (1) tofacitinib 5 mg BID, (2) tofacitinib 10 mg BID, (3) placebo BID → tofacitinib 5 mg BID at Month 3 or 6, (4) placebo BID → tofacitinib 10 mg BID at Month 3 or 6. Advancement from placebo to tofacitinib occurred at Month 3 for the non-responders; all remaining placebo-treated patients were advanced at Month 6. In order to maintain the blind, non-responders on tofacitinib were also 'advanced' although the dose received did not change.

Blinding (masking)

This study was patient, investigator and Sponsor-blinded.

Statistical methods

The approach to control the Type I error is the same step down procedure for the 2 doses. The same methods to analyse the primary variables were used. The Applicant stated that the randomisation is in the ratio 4:4:1:1 with the higher number of patients being randomised to active treatment throughout, and the lower number to placebo before crossing to tofacitinib.

Results

Participant flow

Table 76

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Screened: 1281				
Assigned to Study Treatment	318	318	79	80
Treated	315	318	79	80
Completed	261 (82.1)	252 (79.2)	71 (89.9)	67 (83.8)
Discontinued	54 (17.0)	66 (20.8)	8 (10.1)	13 (16.3)
Patient Died[a]	0	2 (0.6)	0	0
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[b]	1 (0.3)	2 (0.6)	0	1 (1.3)
Not Related to Study Drug	23 (7.3)	30 (9.4)	5 (6.3)	9 (11.3)
Adverse event	6 (1.9)	9 (2.8)	2 (2.5)	3 (3.8)
Lost to follow-up	1 (0.3)	2 (0.6)	2 (2.5)	0
Other [b]	8 (2.5)	14 (4.4)	1 (1.3)	5 (6.3)
Patient no longer willing to participate in study	8 (2.5)	5 (1.6)	0	1 (1.3)

Recruitment

First Subject First Visit: 12 May 2009
Last Subject Last Visit: 17 January 2011

Conduct of the study

Table 77 A3921046 Protocol Deviation Summary Table

	Placebo/ CP-690,550 5 mg BID	Placebo/ CP-690,550 10 mg BID	CP-690,550 5 mg BID / CP-690,550 5 mg BID	CP-690,550 10 mg BID / CP-690,550 10 mg BID	Screen Failure	Total
Concomitant Medication*	7	6	29	22	0	**64**
Inclusion/Exclusion Criteria	11	10	22	29	21	**93**
Informed Consent	8	5	35	28	32	**108**
Investigational Product**	5	4	27	20	0	**56**
Laboratory	20	20	81	67	5	**193**
Other	0	0	0	1	0	**1**
Procedures/Tests	8	25	74	58	10	**175**
Protocol Specific Discontinuation Criteria	0	1	0	2	0	**3**
Safety Reporting	0	0	2	0	0	**2**
Visit Schedule	5	3	11	9	1	**29**
Grand Total	**64**	**74**	**281**	**236**	**69**	**724**

**Concomitant medications include prohibited medications and rescue errors affecting the efficacy of primary endpoints before month 6.*
*** Investigational product includes advancement errors and interrupting study medication before month 6.*
Source: Appendix 3 Table 16.2.2a Protocol Deviations with Drug Assignment for A3921046
Abbreviations: BID=twice a day, mg=milligram, ,

Baseline data

Table 78 Baseline Characteristics

Baseline Characteristic Parameter	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Disease duration (rheumatoid arthritis) (duration since first diagnoses, years):				
N	315	318	79	80
Mean	8.1	9.2	9.5	10.2
Range	0.2-39.9	0.2-41.0	0.3-39.3	0.3-49.0
Rheumatoid factor, n (%):				
N	307	313	78	79
Negative	80 (26.06)	85 (27.16)	21 (26.92)	22 (27.85)
Positive	227 (73.94)	228 (72.84)	57 (73.08)	57 (72.15)
Anti-CCP, n (%):				
N	309	316	78	80
Negative (<20 units)	72 (23.30)	75 (23.73)	19 (24.36)	19 (23.75)
Weak positive (20-39 units)	10 (3.24)	19 (6.01)	2 (2.56)	5 (6.25)
Moderate positive (40-59 units)	12 (3.88)	12 (3.80)	3 (3.85)	2 (2.50)
Strong positive (≥60 units)	215 (69.58)	210 (66.46)	54 (69.23)	54 (67.50)
DAS28-3(CRP):				
N	312	315	79	79
Mean (SD)	5.21 (0.92)	5.26 (0.96)	5.34 (0.85)	5.09 (0.97)
Range	1.60-7.62	2.64-7.66	3.51-7.11	2.58-7.37
DAS28-4(ESR):				
N	309	313	79	79
Mean (SD)	6.29 (0.96)	6.36 (1.01)	6.44 (0.90)	6.16 (0.92)
Range	2.68-8.86	3.00-9.03	4.68-8.51	3.92-8.60
HAQ-DI:				
N	311	315	79	78
Mean (SD)	1.44 (0.69)	1.43 (0.68)	1.45 (0.64)	1.24 (0.66)
Range	0-3.00	0-3.00	0-2.88	0-2.88
Tender joint counts:				
N	312	315	79	79
Mean (SD)	25.00 (15.26)	26.57 (16.10)	27.23 (16.78)	21.86 (13.01)
Range	4.00-68.00	4.00-68.00	5.00-68.00	5.00-67.00
Swollen joint counts:				
N	312	315	79	79
Mean (SD)	14.49 (10.26)	14.41 (9.72)	14.58 (9.65)	13.91 (8.62)
Range	4.00-56.00	4.00-54.00	4.00-56.00	4.00-51.00
ESR (mm/Hr):				
N	311	315	79	79
Mean (SD)	50.46 (28.71)	51.94 (28.46)	51.04 (23.72)	49.29 (27.72)
Range	5.00-150.00	2.00-130.00	6.00-114.00	12.00-116.00
CRP (mg/L):				
N	312	313	79	79
Mean (SD)	17.68 (21.44)	17.73 (21.88)	16.88 (16.47)	16.54 (18.20)
Range	0.30-168.00	0.20-149.00	0.53-92.80	0.36-85.50

Source: Tables 14.1.2.1.3, 14.1.2.1.4, 14.1.2.2, 14.2.4.2, 14.2.5.2, 14.2.6.2, 14.2.7.2, 14.2.11.1.2, 14.2.12.1.2, and 14.2.13.1.2.
Abbreviations: BID = twice daily, CCP = cyclic citrullinated peptide, CRP = C-reactive protein, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, HAQ-DI = Health Assessment Questionnaire - Disability Index, N = number of patients, n = number of patients meeting prespecified criteria, SD = standard deviation

Prior treatment and concomitant medications

Table 79 Previously Taken TNF Inhibitors

Parameters	CP-690,550 5 mg BID N=315 n	CP-690,550 10 mg BID N=318 n	Placebo → CP-690,550 5 mg BID N=79 n	Placebo → CP-690,550 10 mg BID N=80 n
No. of patients with any drug treatment	23 (7.3)	19 (6.0)	5 (6.3)	5 (6.3)
Adalimumab	8	10	2	2
Certolizumab pegol	1	0	0	0
Etanercept	11	7	1	3
Golimumab	2	1	1	0
Infliximab	6	6	1	2

Source: Table 14.4.2.2.2
World Health Organization Drug (Version 02Q2) coding dictionary was applied.
Abbreviations: BID = twice daily, TNF = tumor necrosis factor, No. = number, n = number of subjects meeting criterion
CP-690,550 5 mg BID or CP-690,550 10 mg BID subjects received this dose from Day 1; Placebo -> 5 mg BID or Placebo -> 10 mg BID subjects received Placebo from Day 1 to either Month 3 or Month 6 then changed to either CP-690,550 5 mg BID or CP-690,550 10 mg BID

Table 80 Patients Taking Biologic DMARDs Other than TNF Inhibitors Prior to Screening

Parameter	CP-690,550 5 mg BID N=315 n	CP-690,550 10 mg BID N=318 n	Placebo → CP-690,550 5 mg BID N=79 n	Placebo → CP-690,550 10 mg BID N=80 n
Patients taking biologic DMARDs other than TNF inhibitors prior to Screening				
No. (%) of patients with any drug treatment	7 (2.2)	10 (3.1)	6 (7.6)	0
Abatacept	1	5	3	0
Barninercept	0	1	1	0
Canakinumab	1	1	0	0
Rituximab	3	2	1	0
Tocilizumab	2	2	1	0

Source: Table 14.4.2.2.3
World Health Organization Drug (Version 02Q2) coding dictionary applied.
Abbreviations: DMARD = disease-modifying antirheumatic drug, ATC2 = Anatomical Therapeutic Chemical Classification, BID = twice daily, N = number of patients, n = number of patients meeting prespecified criteria, No. = number
CP-690,550 5 mg BID or CP-690,550 10 mg BID subjects received this dose from Day 1; Placebo -> 5 mg BID or Placebo -> 10 mg BID subjects received Placebo from Day 1 to either Month 3 or Month 6 then changed to either CP-690,550 5 mg BID or CP-690,550 10 mg BID

Table 81 Patients Taking Traditional DMARDs Prior to Screening

Parameter	CP-690,550 5 mg BID N=315 n	CP-690,550 10 mg BID N=318 n	Placebo → CP-690,550 5 mg BID N=79 n	Placebo → CP-690,550 10 mg BID N=80 n
Patients taking traditional DMARDs prior to Screening				
No. (%) patients with any drug treatment	315 (100)	318 (100)	78 (98.7)	80 (100)
Auranofin	0	1	0	0
Chloroquine	8	14	3	5
Chloroquine phosphate	5	1	2	0
Gold	0	2	0	0
Hydroxychloroquine	38	30	8	12
Hydroxychloroquine phosphate	10	11	3	4
Hydroxychloroquine sulfate	9	7	3	2
Leflunomide	99	99	20	19
Methotrexate	259	256	63	63
Methotrexate sodium	14	7	3	3
Penicillamine	4	2	0	1
Sodium aurothiomalate	2	2	0	0
Sulfasalazine	57	73	16	19

Source: Table 14.4.2.2.4
World Health Organization Drug (Version 02Q2) coding dictionary applied.
Abbreviations: DMARD = disease-modifying antirheumatic drug, ATC2 = Anatomical Therapeutic Chemical Classification, BID = twice daily, N = number of patients, n = number of patients meeting prespecified criteria, No. = number
CP-690,550 5 mg BID or CP-690,550 10 mg BID subjects received this dose from Day 1; Placebo -> 5 mg BID or Placebo -> 10 mg BID subjects received Placebo from Day 1 to either Month 3 or Month 6 then changed to either CP-690,550 5 mg BID or CP-690,550 10 mg BID

Table 82 Concomitant DMARD Therapies

No. (%) of Patients	CP-690,550 5 mg BID N=318	CP-690,550 10 mg BID N=318	Placebo → CP-690,550 5 mg BID N=79	Placebo → CP-690,550 10 mg BID N=80
Page 2 of 2				
Leflunomide methotrexate sodium	1	2	0	0
Leflunomide methotrexate sodium aurothiomalate	1	0	0	0
Leflunomide/methotrexate/sulfasalazine	3	4	0	1
Leflunomide/pnicillamine	1	1	0	0
Leflunomide/sodium aurothiomalate/sulfasalazine	0	1	0	0
Leflunomide sulfasalazine	3	3	1	0
Methotrexate/penicillamine	2	0	0	0
Methorexate/sodium aurothiomalate/sulfasalazine	0	1	0	0
Methotrexate/sulfasalazine	17	21	6	10
Single Medication				
No. (%) patients with any concomitant drug treatment	210 (66.0)	206 (64.8)	58 (73.4)	50 (62.5)
Chloroquine	1	2	1	0
Chloroquine phosphate	2	0	0	0
Hydroxychloroquine	4	5	3	6
Hydroxychloroquine phosphate	2	5	1	1
Hydroxychloroquine sulfate	1	0	0	0
Leflunomide	36	27	8	4
Methotrexate	151	150	40	34
Methotrexate sodium	8	3	3	3
Sodium aurothiomalate	1	0	0	0
Sulfasalazine	4	14	2	2

Source: Table 14.4.2.5.9.3 and 14.4.2.5.9.4
Abbreviations: BID = twice daily, No. = number

Numbers analysed

Table 83

No. (%) of Patients	CP-690,550 5 mg BID	CP-690,550 10 mg BID	Placebo → CP-690,550 5 mg BID	Placebo → CP-690,550 10 mg BID
Assigned to Study Treatment	318	318	79	80
Treated	315[a]	318	79	80
Completed	261 (82.1)	252 (79.2)	71 (89.9)	67 (83.8)
Discontinued	54 (17.0)	66 (20.8)	8 (10.1)	13 (16.3)
Analyzed for Efficacy:				
Full Analysis Set	312 (98.1)	315 (99.1)	79 (100)	79 (98.8)
Per Protocol Analysis Set	296 (93.1)	298 (93.7)	76 (96.2)	72 (90.0)
Analyzed for Safety:				
Adverse events	315 (99.1)	318 (100)	79 (100)	80 (100)
Laboratory data	315 (99.1)	313 (98.4)[b]	79 (100)	80 (100)

Outcomes and estimation

Primary endpoints

1. ACR 20 responses at month 6

Table 84 Normal Approximation to ACR20 Response Rates at Month 6 (FAS, NRI, Comparisons to Placebo)

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

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

2. HAQ-DI at month 3

Table 85 Summary of LS Mean Changes from Baseline in HAQ-DI at Month 3 (FAS, Differences From Placebo)

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

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

3. DAS28(ESR) <2.6 at month 6

Table 86 Summary of Patients Achieving DAS28-4(ESR) <2.6 at Month 6 (FAS, No Imputation, Comparisons to Placebo)

Treatment	N	n	%	Difference from Comparator			
				Difference	95% CI for Difference		P-value
					Lower	Upper	
CP-690,550 5 mg BID	241	33	13.69	8.54	2.83	14.25	0.0033
CP-690,550 10 mg BID	248	41	16.53	11.38	5.45	17.31	0.0001
Placebo	136	7	5.15	Not applicable			

Source: Table 14.2.13.4.5
Abbreviations: BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, FAS = full analysis set, N = number of patients, n = number of patients meeting prespecified criteria, CI = confidence interval

Secondary endpoints

Improvements over time, in a dose-dependent fashion, were observed for ACR50, ACR70, and in the change from baseline in DAS28-4(ESR). Treatment with tofacitinib (5 and 10 mg BID) was effective compared with placebo in improving secondary endpoints of signs and symptoms of RA in patients with RA (change from baseline in DAS28-4[ESR] and DAS28-3[CRP]) through Month 6. Statistically significant differences from placebo were demonstrated as early as Week 2 for ACR20, ACR50, ACR70 and HAQ-DI.

Patients treated with tofacitinib 10 mg BID generally showed numerically greater ACR20/50/70 response rates, and improvements from Baseline in DAS28 and HAQ-DI, compared with those treated with tofacitinib 5 mg BID. Efficacy responses were sustained in the tofacitinib 5 and 10 mg BID treatment groups through Month 12.

Patients who received placebo for 3 to 6 months and then advanced to tofacitinib treatment (5 mg or 10 mg BID) showed improvement in all efficacy measures (ACR20, ACR50, ACR70, HAQ-DI, DAS28-3[CRP], and DAS28-4[ESR]).

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 87: 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 tofacitinib 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:	3 to 6 months in DB (end of PC phase)			
	Duration of Extension phase:	6 months in DB extension period			
Hypothesis	This protocol is designed to establish the superiority of two doses (5 and 10 mg BID) oftofacitinib to placebo for all three primary endpoints				
Treatments groups	tofacitinib 5 mg BID (sequence 1)	N=204, 12 months			
	Tofacitinib 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			

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 (tofacitinib), adalimumab or placebo.				
Descriptive statistics and estimate variability	Treatment group	tofacitinib 5 mg BID	tofacitinib 10 mg BID		placebo → tofacitinib 5 or 10 mg
	Number of subject FAS	201	199		107
	ACR 20 responder rate at month 6	51.53% (N=196)	52.55% (N=196)		28.30% (N=106)
	HAQ-DI change at month 3 (LS mean)	-0.55 (N=188)	-0.61 (N=185)	)	-0.24 (N=98)
	DAS28-4 (ESR) <2.6 at month 6	7.34 % (N=177)	12.50% (N=176)		1.09% (N=92)
Effect estimate per comparison	**ACR 20 responder rate at month 6**	**Comparison with placebo**		**tofacitinib -5 mg BID**	**tofacitinib -10 mg BID**

		Difference versus placebo	23.22	24.24
		95% CI for difference	12.16, 34.29	13.18, 35.31
		P-value	<0.0001	<0.0001
	HAQ-DI change at month 3 (LS mean)	**Comparison with placebo**	**tofacitinib-5 mg BID**	**TOFACITINIB-10 mg BID**
		Difference versus placebo	-0.31	-0.38
		95% CI for difference	-0.43, -0.19	-0.50, -0.25
		P-value	<0.0001	<0.0001
	DAS28-4 (ESR) <2.6 at month 6	**Comparison with placebo**	**TOFACITINIB-5 mg BID**	**TOFACITINIB-10 mg BID**
		Difference versus placebo	6.25	11.41
		95% CI for difference	1.86, 10.64	6.08, 16.73
		P-value	0.0051	<0.0001
Analysis description	**Secondary analysis : comparison with adalimumab**			
	ACR 20 responder rate at month 6	**Comparison with ADA**	**TOFACITINIB-5 mg BID**	**TOFACITINIB-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**	**TOFACITINIB-5 mg BID**	**TOFACITINIB-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**	**TOFACITINIB-5 mg BID**	**TOFACITINIB-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 88: Summary of efficacy for trial A3921045

Title: Phase 3, Randomized, Double Blind, Placebo Controlled Study of the Efficacy and Safety of 2 Doses of tofacitinib 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 tofacitinib in a blinded fashion at either 5 mg or 10 mg for the remainder of the 6-month study

	Duration of main phase:		3 month
Hypothesis	Superiority		
Treatments groups	tofacitinib 5 mg BID (sequence 1)		N= 244, 6 month duration
	tofacitinib 10 mg BID (sequence 2)		N= 245, 6 month duration
	placebo →tofacitinib 5 mg (sequence 3)		N=61, 3 month
	placebo →tofacitinib 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	

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	tofacitinib 5 mg BID	tofacitinib 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	tofacitinib 5 mg BID	tofacitinib 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	tofacitinib 5 mg BID	tofacitinib 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	tofacitinib 5 mg BID	tofacitinib 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

Table 89: 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 tofacitinib 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 TOFACITINIB 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 (tofacitinib 5 mg BID, tofacitinib 10 mg BID, placebo to tofacitinib 5 mg BID, placebo to tofacitinib 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	tofacitinib 5 mg BID (sequence 1)		321, 12 month	
	tofacitinib 10 mg BID (sequence 2)		319, 12 months	
	placebo → tofacitinib 5 mg (sequence 3)		81, 3 to 6 months	
	placebo → tofacitinib 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		

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**	**tofacitinib 5 mg BID**	**tofacitinib 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**	**tofacitinib 5 mg BID**	**tofacitinib 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	-0.79, -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			

Table 90: 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 tofacitinib 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) tofacitinib 5 mg BID, (2) tofacitinib 10 mg BID, (3) placebo BID→ tofacitinib 5 mg BID at Month 3, (4) placebo BID → tofacitinib 10 mg BID at Month 3. Following 3 months of treatment, patients who first received placebo switched to tofacitinib 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:	3 months (PC period) 3 month	
Hypothesis	Superiority versus placebo		
Treatments groups	tofacitinib 5 mg BID (sequence 1)	N=133, 6 months	
	tofacitinib 10 mg BID (sequence 2)	N=134, 6 months	
	placebo →tofacitinib 5 mg (sequence 3)	N=66, 3 months	
	placebo →tofacitinib 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	
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**	**tofacitinib 5 mg BID**	**tofacitinib 10 mg BID**	
	Number of subject	131	132	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		**tofacitinib 5 mg BID**	**tofacitinib 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		**tofacitinib 5 mg BID**	**tofacitinib 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		**tofacitinib 5 mg BID**	**tofacitinib 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

Table 91: 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 tofacitinib 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 558 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) tofacitinib 5 mg BID, (2) tofacitinib 10 mg BID, (3) placebo BID →tofacitinib 5 mg BID at month 3 or 6, (4) placebo BID → tofacitinib 10 mg BID at month 3 or 6. Advancement from placebo to tofacitinib occurred at month 3 for the non responders; all remaining placebo-treated patients were advanced at Month 6	
	Duration of main phase: Duration of Run-in phase:	6 months 6 months
Hypothesis	Superiority versus placebo	
Treatments groups	tofacitinib 5 mg BID (sequence 1)	N=315, one year
	tofacitinib 10 mg BID (sequence 2)	N=318, one year

	placebo → tofacitinib 5 mg (sequence 3)		N=79, 3 to 6 months
	placebo → tofacitinib 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	

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**	**tofacitinib 5 mg BID**	**tofacitinib 10 mg BID**
	Number of subject	157	311	309
	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	**tofacitinib 5 mg BID**	**tofacitinib 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	-0.44, -0.26
		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 performed across trials (pooled analyses and meta-analysis)

Current pharmacological therapies include traditional disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents. In order to better understand the relative efficacy and safety of tofacitinib to alternative RA therapies, a Bayesian mixed treatment comparison was conducted to evaluate multiple endpoints in two separate populations including RA patients who have had an inadequate response to: (1) a traditional DMARD (DMARD-IR); and (2) a TNF inhibitor (TNF-IR).

The objectives of the study were to estimate the relative efficacy and safety of tofacitinib 5 mg and 10 mg BID versus biologics in combination with MTX or as monotherapy, used in the treatment of:

1) Adult RA patients who inadequately responded to treatment with traditional DMARDs

2) Adult RA patients who inadequately responded to treatment with TNF inhibitors.

A systematic literature review was performed in Medline and Embase to identify RCTs concerning the efficacy and safety of tofacitinib, TNF inhibitors and other biologics for RA in DMARD-IR and TNF-IR patients. In total, 47 publications were identified, 39 concerning DMARD-IR patients and 8 concerning TNF-IR patients. The applicant provided 2 submitted articles based on phase II trials (Kremer et al, 2010 and Fleischmann et al, 2010), 4 phase III trial data reports concerning DMARD-IR patients (A3921045; A3921044; A3921046; A3921064), and one phase III trial data report concerning TNF-IR patients (A3921032). The 45 publications and data reports relevant for the DMARD-IR population described 31 trials and the 9 publications and data report relevant for the TNF-IR population described 5 trials.

Given the heterogeneity of included studies with regards methodology, inclusion criteria, baseline characteristics and disease, percentage of discontinuation, the CHMP considered that no firm conclusions can be drawn from this meta-analysis and that it can be seen as supportive only.

Supportive studies

A391069

The one-year analysis report of the tofacitinib monotherapy versus methotrexate study A3921069 was provided by the applicant during the review of the application.

Study A3921069 was a Phase 3 randomized, 24-month, double-blind, parallel-group study, to investigate the efficacy and safety of tofacitinib monotherapy in the treatment-naïve population.

Male and female patients at least 18 years of age, with a diagnosis of rheumatoid arthritis (RA), with evidence of disease activity by swollen and tender joint counts and laboratory markers of inflammation, were enrolled in the study. Patients were required to have 1 of the following: erythrocyte sedimentation rate (ESR) >28 mm/hr in the local laboratory or Creactive protein (CRP) >7 mg/L in the central laboratory. Exclusionary criteria included active or latent or inadequately treated infection with *Mycobacterium tuberculosis* (TB).

Other exclusion criteria included pregnancy, blood dyscrasias, or any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may have increased the risk associated with study participation or investigational product administration or may have interfered with the interpretation of study results and, in the judgment of the investigator, would have made the patient inappropriate for entry into this study. Patients were not eligible if they had received more than 3 weekly doses of methotrexate (MTX) or, if less were received, the MTX was stopped due to AE attributed to MTX.

Patients were randomized in a 2:2:1 ratio to 1 of the following 3 parallel treatment arms:

- Tofacitinib 5 mg twice daily (BID) (tablets);
- Tofacitinib 10 mg BID (tablets);
- Methotrexate 10 mg/week (wk) to 20 mg/wk (capsules), titrated as follows:

  - 10 mg once weekly for 4 weeks; if well-tolerated was to be titrated up to:
  - 15 mg once weekly for 4 weeks; if well-tolerated was to be titrated up to:
  - 20 mg once weekly for duration of study.

One dose reduction in MTX, of 5 mg/wk, was allowed for lack of tolerance as long as patients stayed on at least 10 mg MTX or placebo (4 capsules) weekly. Division of weekly doses into 2 or 3 fractions, delivered approximately 12 hours apart, was allowed after Visit 3 (Month 2) for lack of tolerance.

Patient Disposition

Nine hundred fifty-eight (958) patients were randomized to treatment, and 952 received at least 1 dose of study medication. Three patients each in the tofacitinib 5 mg BID and 10 mg BID groups were randomized but not treated.

At the 1-year cut-off point, based on patient status case report forms (CRFs), 769 treated patients overall were ongoing in the study; the MTX group had the highest rate of patients who discontinued (52 patients, 28.0%). Based on patient status CRFs, a total of 58 (6.1%) treated patients withdrew due to adverse events (AEs) (41 of these patients had AEs considered related to study drug and 17 of these patients had AEs considered not related to study drug). Discontinuations related to study drug whether due to AE or lack of efficacy were more common in the MTX group. Two patients, both in the tofacitinib 5 mg BID group, were withdrawn due to pregnancy within the data cut-off date for the 1-year analysis.

Analysis of efficacy

mTSS at Month 6 (1-Year Analysis)

Table 100 **Summary of LS Mean Changes From Baseline in Modified Total Sharp Scores (mTSS) at Month 6 (FAS, LEP, 1-Year Analysis)**

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

ACR70 at Month 6 (1-Year Analysis)

Table 101 **Normal Approximation to ACR70 Response Rates at Month 6 (FAS, NRI, Differences From MTX, 1-Year Analysis)**

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

A3921024

Study A3921024 is a Phase 2/3 long-term, open-label follow-up study to evaluate the long-term safety of patients on 5 or 10 mg BID of tofacitinib with a secondary objective of evaluating sustained efficacy in patients with RA. Patients who have completed participation in a randomized study of tofacitinib for the treatment of RA are eligible to join. The study remains ongoing.

A3921041

This is a Phase 3, long-term, open label, multicenter, extension study to evaluate the long-term safety of patients on 5 or 10 mg BID of tofacitinib with a secondary objective of evaluating sustained efficacy in patients with RA. Eligible Japanese patients who had completed a tofacitinib RA study (Studies A3921039, 1040, and patients from 1044 study sites in Japan) were enrolled. The study remains ongoing.

2.5.3. Discussion on clinical efficacy

Study A3921064

This study included an active comparator treatment arm, adalimumab, dosed as 40 mg SC injections q 2 weeks. Anti-TNF alpha inhibitors are considered as “gold standard” in second line indication for the treatment of RA patients. Therefore, the choice of adalimumab as active comparator is endorsed by the CHMP. However, tofacitinib was not compared to adalimumab (it was not a superiority study nor non-inferiority study), as the study was designed to establish the superiority of 5 and 10 mg BID as compared to placebo.

Treatment groups were well balanced for baseline demographics and clinical characteristics. Overall, included patients had moderate to severe RA at baseline.

98.2% of patients were on concomitant background MTX. However, 51 (7%) among them were previously treated with biologic DMARDS (mainly anti-TNF agents) whereas previous biologic DMARDs treatment was an exclusion criteria. In addition, the CHMP noted that the duration since first diagnoses was too short for some patients to consider them as having an inadequate response to MTX for this study.

The three primary endpoints (ACR 20 response rate at month 6, improvement in HAQ-DI at month 3 and DAS 28-4(ESR) <2.6 at month 6) were achieved to a statistical level.

Indirect comparisons with adalimumab suggested that efficacy is similar between both tofacitinib groups and adalimumab for improvement in signs and symptoms and in physical function.

Overall, although not powered for statistical comparisons, the data from the active comparator arm suggests that tofacitinib 5 mg dose mg BID has a similar effect like adalimumab (both in combination with MTX) in terms of signs and symptoms and improvement in physical function.

Study A3921045

Treatment groups were well balanced for baseline demographics and characteristics. Overall, patients had moderate to severe RA at baseline. The primary endpoints were the same than those used in study 1064 but ACR 20 response rate and DAS 28 were assessed at month 3 instead of month 6 (due to ethical reason since patients were not received background MTX).

In this study only 16.2% had prior TNFi exposure. Given that a majority of patients were in failure of MTX, the study is only considered relevant for a second line indication, i.e. after failure to traditional DMARDs. However, as no appropriate comparator was included, the study does not strictly comply with regards to a second line indication either. The CHMP advice clearly stated that a 2nd line monotherapy indication would require comparative data with a TNFi/bDMARD, which was not adhered to in the study design. In addition, the CHMP noted that the duration since first diagnoses was too short for some patients to consider them as having an inadequate response to MTX for this study.

The proportion of patients achieving an ACR 20 response at month 3 was significantly higher in the tofacitinib 5 and 10 mg groups, than in the placebo group (60 %, 65.7% and 26.6% of patients respectively).

Physical function assessed by HAQ-DI response rate at 3 month demonstrated statistically significant differences in tofacitinib 5 and 10 mg groups as compared with placebo (LS mean changes from baseline -0.50, -0.57 and -0.19, respectively). However, the last co-primary endpoint DAS28<2.6 was not statistically significant, neither for the tofacitinib 5 mg group nor for the 10 mg group.

This was the only trial to support the monotherapy indication. Although the Applicant designed the error control strategy such that the trial is not formally considered a failure, given that both doses failed for

DAS28 in the monotherapy setting, the totality of the evidence for efficacy in monotherapy is considered weak for both doses.

The placebo response rate is similar to study A3921046, but the active response rates are much lower. In contrast, studies A3921032 and A3921044 had a much lower placebo response rate but a similar or higher proportion of responders on active. Therefore it is not just a higher than expected placebo response or a lower than expected active response that is driving this lack of significance. These results are particularly surprising in light of the similar ACR20 and HAQ-DI data.

Study 1044

The main objectives of this study were to assess sign and symptoms in patients with active RA on a stable background of MTX (as measured ACR20 response rates at month 6), inhibition of structural damage (as measured by changes from baseline using the van der Heijde modified Sharp score at month 6), improvement in physical function (as measured by HAQ-DI at month 6) and low disease activity (as measured by DAS28-4 (ESR) <2.6). Due to the design of the study, around half of the placebo patients only had data until month 3 when they switched to active. Therefore their month 6 values had to be extrapolated.

Treatment groups were well balanced for baseline demographics and disease characteristics. The mean time from diagnosis of RA to inclusion in the study ranged from 8.8 years to 9.5 years across the 4 treatment groups.

The proportions of patients with positive anti-CCP at Baseline ranged from 82.28% to 85.94% across treatment groups. Mean mTSS scores at baseline were also similar. Overall, included patients had moderate to severe active RA at inclusion.

There were 4 primary endpoints assessed sequentially using a step-down approach where statistical significance could be claimed for second endpoint only if the first endpoint in the sequence met the requirements for significance: 1) ACR 20 at Month 6; 2) total modified Sharp score (mTSS) change from baseline at month 6; 3) HAQ-DI change from baseline at month 3; 4) DAS28-4 (ESR) <2.6 at Month 6.

ACR 20 response was statistically significant at month 6 for both tofacitinib group, whereas the secondary primary endpoint, i.e. the reduction in mTSS at 6 month for the 5 mg dose did not reach statistical significance (p=0.0792). The difference was only statistically significant for the 10 mg dose (p=0.0376) at month 6 and at month 12. Furthermore, due to the linear extrapolation used to handle missing data, it is likely that the treatment effect has been overestimated.

In conclusion, study 1044 was mainly designed to support the claim “inhibition of structural damage”. Although one of the primary endpoint (ACR 20 response rate) was statistically significant as compared with placebo, this study is considered as negative due to the lack of efficacy on structural damage. Indeed, the primary endpoint (reduction from baseline in mTSS at 6 month) was not statistically different from placebo for the tofacitinib 5 mg BID. The data provided including various sensitivity analyses (based on linear extrapolation for missing data) indicated that efficacy with regards to inhibition of structural damage is only borderline for 10 mg and has not been robustly demonstrated for the 5 mg dose. In patients who advanced from placebo to tofacitinib, there appeared to be some slowing of progression, but given the design of the trial it is difficult to quantify the magnitude of the effect.

Due to the hierarchical nature of the Type I error control, it cannot formally be concluded that efficacy has been demonstrated for HAQ-DI and DAS28.

Study 1032

All patients had received at least 1 DMARD prior to enrolling in the study. 100% patients had taken MTX before screening. 99.2% patients had taken TNF inhibitors before inclusion. The majority of patients

(64%) had been previously treated with a single TNF inhibitor (mainly adalimumab and etanercept) with similar proportions across treatment groups. 27% of patients had received previous treatment with 2 TNF inhibitors and 8% had been previously treated with 3 or more. The mean number of previously tried TNF inhibitors was comparable across treatment groups and ranged from 1.43 to 1.51. The maximum number of previously tried TNF inhibitors was 4. In addition, concerning the treatment with other previous drugs, the CHMP noted that the duration since first diagnoses was too short for some patients to consider them as having an inadequate response to MTX for this study.

Treatments groups were well balanced for baseline demographics and clinical characteristics. Patients generally have long standing disease (mean time from diagnosis of RA ranged from 11.2 years to 13.0 years) and severe uncontrolled activity disease at baseline.

The 3 primary endpoints (ACR20 response rate at month 3, changes from baseline in HAQ-DI at month 3 and rate of patients achieving DAS28-4(ESR) <2.6 at month 3) were achieved to a statistical level.

Subgroup efficacy analyses have shown that approximately 65% of patients had discontinued their anti-TNF treatment due to lack of efficacy, while approximately 13.8% and 19.5% discontinued treatment due to an AE or both loss of efficacy and an AE, respectively.

The ACR 20 response rate at 3 months in patients who had lack of efficacy to anti-TNF agents were 40.66% in the tofacitinib 5 mg group, 46.51% in the tofacitinib 10 mg group and 26.51% in the placebo group ($p<0.05$).

The ACR 20 response rate at 3 months in patients who had failed to anti-TNF agents due to AEs were 23.53% in the tofacitinib 5 mg group, 57.89% in the tofacitinib 10 m group and 21.05% in the placebo group.

Therefore, it seems that the reason for inadequate response (intolerance or lack of efficacy) to previous anti-TNF inhibitors could have an impact on the tofacitinib 5 mg efficacy response.

This study was intended to support the third line indication (i.e., after failure to anti-TNF inhibitors). It was noted by the CHMP that treatment failure to anti-TNF alpha for lack of efficacy or intolerance was not defined in the SAP and was based only on the opinion of the investigator, which is subjective.

Study 1046

Treatments groups were well balanced for baseline demographics and clinical characteristics.

The three primary endpoints (ACR 20 response at month 6, HAQ-DI at month 3, DAS28-4 (ESR) at month 6) were met to a statistical level.

Study 1069

In answer to questions raised by the CHMP concerning the beneficial effect on structural damage, the applicant provided the preliminary results of the study 1069. Results of this study showed efficacy on structural damage, however, the studied population was a MTX naïve-population which is not the population in which the indication was sought.

Thus the data provided to date are not considered appropriate to support the efficacy of tofacitinib 5 mg BID on structural damage in the target population.

Additional expert consultation

During the procedure at the CHMP's request an ad-hoc expert group meeting was organized. The responses to the three questions asked to the experts by the CHMP are reproduced below.

1. Based on the available data, conclusive efficacy has been demonstrated on treatment of RA symptoms but not on prevention of structural damage. Do the experts consider the available evidence sufficient for the approval of tofacitinib in terms of its efficacy in the treatment of moderate to severe active RA?

The experts expressed the view that, to be qualified as a DMARD, tofacitinib is required to show inhibition of signs and symptoms of the disease as well as prevention of structural damage in the proposed patient population of interest.

There was a consensus amongst the experts that the efficacy of tofacitinib (5 and 10 mg) has been demonstrated with regard to its effects on signs and symptoms of RA. The experts considered that the 10 mg dose of tofacitinib (which is no longer being proposed by the applicant for licensing as a treatment of RA) has shown evidence for the prevention of structural damage. However, for the lower 5 mg dose the experts agreed that prevention of structural damage in the proposed DMARD failure population had not been adequately demonstrated.

The experts also took note of the new available data on inhibition of structural damage in MTX-naïve patients (which is not the population in which the indication is being claimed by the applicant). There was a unanimous view that extrapolation of data from MTX-naive patients to the proposed DMARD failure population is not appropriate to support the demonstration of prevention of structural damage as MTX naïve patients tend to respond better than MTX-resistant patients. Therefore the experts unanimously considered that the clinical efficacy of tofacitinib in the prevention of structural damage has not been adequately demonstrated by the applicant for the applied dose of the 5 mg in the applied the proposed DMARD failure population.

The group acknowledged the favourable data on patient reported outcomes and agreed that tofacitinib had shown superiority vs. placebo in several parameters including pain, HAQ-DI, SF-36 PCS and fatigue scores.

2. Tofacitinib is a potent immunosuppressive drug which acts as an inhibitor of JAK-3 causing pervasive immunosuppression, and in particular affecting T-cell development and maturation. The development programme highlights NK cell decreases at 6 weeks and CD4/8 cell decreases at 6 months. The CD4/8 cell decreases are persistent. In addition:

- **Reversibility of pharmacodynamic effect has not been adequately demonstrated.**
- **Functional impairment of the immune system has not been adequately characterised.**
- **Patients developed serious unresolved opportunistic infections including cryptococcal meningitis and P jiroveci pneumonia, in some cases associated with lymphopaenias. The WBC responsible for the lymphopaenias has not been characterised, however the spectrum of infections are suggestive of a cell-mediated immune deficiency.**

a) Is the pharmacodynamic effect of Tofacitinib sufficiently characterized such that the immunosuppression-related adverse effects can be monitored and managed in clinical practice to minimise the risk of adverse effects?

There was a general concern amongst the experts that the pharmacodynamic effect of tofacitinib on the immune system has not been adequately studied by the applicant and the data available to date seems insufficient.

Although the experts acknowledge that the risk of serious infections was more prominent in patients with low lymphocyte count and agreed that the monitoring of lymphocyte count could be considered as a

relevant parameter for these events, they were of the opinion that opportunistic infections cannot be predicted with any certainty since the risk of opportunistic infection does not correlate systematically with the lymphocyte count. Particularly this unpredictability of the risk for opportunistic infection in terms of both possibility for monitoring and timing of event during treatment are detrimental for management in clinical practice. The experts noted that most of these events are reactivation of infections (CMV, pneumocystic carinii…) and that there would be is a need to educate the patients about the symptoms of these opportunistic infections and the need to actively report these to physicians.

The experts discussed whether functional assay (e.g. T-cell subsets or NK cell assays) could be used to identify the patients at risk and agreed that these assays are only available in specialised centres and not in routine clinical practice. Also their value to distinguish reliably the patients at risk was not considered established.

Overall, the experts agreed that it is difficult to predict which patients treated with tofacitinib would be at risk of developing serious and opportunistic infections and concluded that the immunosuppression-related adverse effects will be difficult to manage in clinical practice. It was noted that tofacitinib is an oral tablet formulation which might impact the perception of risk compared to injectable products (IV or SC) hence this needs to be considered for the labelling and the RMP (physician and patient education).

b) Can the experts suggest additional data that can better quantify the above-mentioned risks either pre/post approval?

In general, there was the view that further exploration of the effect of tofacitinib on lymphocyte sub-sets was of little value as it was unlikely to offer any additional information over and above the absolute lymphocyte count, coupled with the difficulty in obtaining lymphocyte subset analysis in routine clinical practice.. Some experts expressed the view that it might be of interest to monitor T-cell subset in a clinical trial situation to further explore effects of this drug in the immune system.

The experts made the suggestion that the company could further characterise the patients at risk of developing opportunistic infections in terms of clinical criteria by assessing their clinical background and all possible confounding factors such as the age, co-morbidities, concomitant treatments (e.g. corticosteroid use, MTX….).

3. Other identified risks of treatment with tofacitinib include gastrointestinal perforations, malignancy and drug-induced liver injury. Taking into account the safety profile of tofacitinib and the limitations to the efficacy data, do the experts see a patient population where tofacitinib would add value to the therapeutic armamentarium? If so, how could this population be defined and are there adequate data in the dossier to support a licensing decision?

The spectrum of other identified risks appeared to be similar to those observed with immunosuppressants and other drugs used in the treatment of RA patients and rheumatologists are familiar with their management.

However, the experts unanimously agreed that taking together the lack of adequate efficacy demonstration on structural damage and the concerns about the safety profile of the product with regard to serious and opportunistic infections and their management in clinical practice, the support for the applied 5 mg dose in the population for the claimed indication is insufficient. Furthermore, the available data does not allow identification of a patient population where tofacitinib would add value to the therapeutic armamentarium already available for the treatment of RA.

2.5.4. Conclusions on the clinical efficacy

Tofacitinib is a new chemical treatment with a different mechanism of action to products already approved for the treatment of rheumatoid arthritis. Therefore, it could represent a therapeutic alternative in some categories of patients. Beyond its mechanism of action, the main interest lies in its oral route of administration, as compared with biologicals administered by SC or IV routes.

Data from five pivotal studies has been provided to support the clinical efficacy of tofacitinib 5mg and 10 mg for the treatment of rheumatoid arthritis in different patient populations. During the assessment, to address safety concerns, the Applicant proposed to restrict the daily dose to 5 mg BID and the indication to patients with inadequate response to at least one biologic disease modifying antirheumatic drug (DMARDs). Taking together the data from these studies, the efficacy demonstration of tofacitinib is not considered fully established as generally consistent results have only been achieved for the improvements of signs and symptoms (ACR 20) and physical function (HAQ-DI). The data on the impact of disease activity (achieving a DAS28 score of <2.6) are not compelling.

A beneficial effect on structural damage could not be demonstrated for the 5 mg dose in the target population. In the pivotal study (study 1044) for the investigation of effect on structural damage, the primary endpoint (mTSS) only reached statistical significance for the higher (10 mg) dose and not the lower (5 mg) dose. In addition, there was concern that the statistical methods employed to handle patients who discontinued from the randomised treatment may overestimate the treatment effect.

Supportive data from another study in MTX-naïve patients, where efficacy on structural damage was shown for both tofacitinib doses, was not considered sufficient by the CHMP to overcome this failure to demonstrate efficacy on structural damage in the proposed target population due to the uncertainty as to whether the data can be extrapolated to the target population as defined by the indication above.

The CHMP therefore concluded that the clinical efficacy of tofacitinib was insufficiently established for the claimed indication and posology in the target patient population.

2.6. Clinical safety

The clinical safety of tofacitinib mainly focused on 4 completed Phase 3 studies, and a Phase 3 study 1-year analysis which included 3315 patients, and 2 ongoing open-label, long-term extension (LTE) studies in 3227 patients, with a data cut-off date of 29 March 2011.

Overall, 4816 patients were included in the clinical part of the development programme across all treatment groups of patients with rheumatoid arthritis. The majority of these patients (4610) were treated with recommended doses of 5 mg or 10 mg BID.

The patient exposure to study drug in completed phase 2 and 3 studies and long term extension studies was 5716 patient years (cut-off date 29th March 2011) for 4816 exposed patients.

Patients with long-term safety data: a total of 3822 patients (cut-of date 29th September 2011) received the 5 mg dose or the 10 mg dose for at least 6 months, 2951 patients received at least 1 year of treatment and 693 patients received at least 2 years of the 5 mg dose or the 10 mg dose treatment. Five patients were treated for 4 years (the 5 mg dose arm).

In the LTE studies, the exposure was greater in the 5 mg dose group with the mean duration of open-label treatment of 612 and 167 days for the 5 mg dose and the 10 mg dose groups, respectively.

Baseline characteristics of patients included in the clinical studies were similarly balanced between the treatment groups. The studies were performed worldwide including the European population (about 1/3) as well as population from other continents (US, Asia, Latin America).

Patients ranged in age from 18 to 86 years. The mean age ranged from 50 to 56 years. No children were included. The majority of patients were female (81-85%) as expected for this pathology. The BMI was about 27 (range 14.3-70.8), including overweight and obese population (weight between 32.4 and 188kg). More than half of the patients were white; one third was from Asia.

About 15% of patients were older than 65 years.

Table 102 Duration of Exposure to CP-690,550 (Any Dose), in Completed Rheumatoid Arthritis Phase 2 and 3 Studies and Long Term Extension Studies

Duration of Exposure (months)[a]	No. of Patients	Duration Interval (months)[b]	Patient-Years for Duration Interval[b]
<1	4816	<1	395.93
≥1	4664	≥1 - <3	740.17
≥3	4213	≥3 - <6	1014.48
≥6	3768	≥6 - <12	1668.25
≥12	2703	≥12 - <18	889.26
≥18	905	≥18 - <24	385.21
≥24	696	≥24	622.73
Total patient-years[c]			*5716.03*

a. Exposure is to any dose of CP-690,550. One month was defined as 30.25 days.
b. Patient-years in each of the duration of exposure rows is incremental and unique; thus does not include the duration (years) of previous time intervals. Patients are counted only once if they participated in both Ph 2 or 3 study and also a long term extension (LTE) study, however their time in both the qualifying and LTE study is included in the person time column.
c. Total patient-years is the sum of patient-years for each duration interval.
Studies included: A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (data up to 1 year), A3921045, A3921046, A3921064.
Source: RMP Table 2.1.

Adverse events

The adverse events are presented in tables summarizing i) the phase 3 background DMARD studies and ii) monotherapy studies, up to 3 months, from 3 to 6 months and above 6 months.

Four (4) phase 3 background DMARD studies were pooled (1032, 1044 (ongoing study), 1046 and 1064); all these studies used placebo as a comparator. One study included an active comparator arm, adalimumab (study 1064).

In the phase 3 background DMARD studies:

- The number of patients with AE, with SAEs or discontinuations was comparable between the study drug (5 and 10 mg BID) and placebo or adalimumab up to 3 months.
- between 3 and 6 months, the number of AEs increased in study drug groups (39.7% and 37.5% for 5 and 10 mg BID) compared to placebo (26.2%) and adalimumab (33.3%) with more temporary discontinuations due to AEs (7.5% and 6.6% for 5 and 10 mg BID groups versus 1.8% and 4.9% for placebo and adalimumab).
- above 6 months of treatment, the number of patients with AEs, SAEs and discontinuations was similar between study drug groups and adalimumab, but still more patients had dose reduction or temporary discontinuation due to AE with study drug (7.3%) compared to adalimumab (2.9%). However, the number of patients is multiplied 10-fold between study drug and comparator: 2102 patients were treated with study drug; 204 with adalimumab.
- up to 3 months, more gastrointestinal disorders and more infections were reported with study drug (15.3% and 21.3%) in comparison to adalimumab (10.3% and 16.2%); hypertension has been observed in 2% of patients treated with study drug while no cases have been reported in adalimumab group.
- the number of infections increased in 5 and 10 mg BID groups between 3 to 6 months of treatment in comparison to placebo and adalimumab: 17%, 9% and 13.7%, respectively. After more than 6 months of treatment, there were slightly more infections in study drug groups (20.5%), compared to

comparator (17.6% in adalimumab group); the number of herpes zoster was the same (2% in each group).

Table 103 **Summary of Treatment-Emergent Adverse Events (All Causality) in Phase 3 Background DMARD Studies (up to 3 Months): Number (%) of Patients**

	CP-690,550				
	5 mg BID	10 mg BID	All Doses	Placebo	Adalimumab
Patients evaluable for adverse events	973	969	1942	559	204
Number of adverse events	1042	1053	2095	563	182
Patients with adverse events	500 (51.4)	514 (53.0)	1014 (52.2)	296 (53.0)	105 (51.5)
Patients with serious adverse events	35 (3.6)	30 (3.1)	65 (3.3)	19 (3.4)	5 (2.5)
Patients with severe adverse events	46 (4.7)	33 (3.4)	79 (4.1)	25 (4.5)	6 (2.9)
Patients discontinued due to adverse events	50 (5.1)	43 (4.4)	93 (4.8)	17 (3.0)	10 (4.9)
Patients with dose reduced or temporary discontinuation due to adverse events [a]	86 (8.8)	83 (8.6)	169 (8.7)	28 (5.0)	15 (7.4)

BID=twice daily.
a. Dose reductions were not permitted in Phase 3 studies.
Except for the total number of adverse events, patients are counted only once per treatment in each row.
Adalimumab treatment is only in Study A3921064.
MedDRA (v13.1) coding dictionary applied.
Includes Protocols A3921032, A3921044 (Year 1 Analysis), A3921046, and A3921064.
Source: P3DMARD Table 4.1.1.

In the monotherapy studies, the number of patients with AEs was comparable between the study drug and placebo with less discontinuation due to AE in the study drug group (1.6% vs. 4.1%) up to 3 months. No significant differences were observed by SOC and PT.

From 3 to 6 months, no comparison with placebo is available. Slightly more patients with AEs were reported with 10 mg BID dose than with 5 mg BID dose, however this difference was not significant.

In the all phase 3 studies, the number of patients with AE or SAE is comparable between study treatment and placebo. Slightly more discontinuations due to AEs and temporary discontinuations or dose reduction with study treatment versus placebo is noted. More patients experienced an AE of infection with study treatment (17.1%) compared to placebo (9%) and adalimumab (13.3%).

Table 104 **Summary of Treatment-Emergent Adverse Events (All Causality) in All Long-Term Extension Studies (All Patients): Number (%) of Patients**

	CP-690,550		
	5 mg BID	10 mg BID	All Doses
Patients evaluable for adverse events	1321	1906	3227
Total pt-yr of drug exposure	2236.4	881.9	3118.3
Number of adverse events	4899	2848	7747
Patients with adverse events	1047 (79.3)	1088 (57.1)	2135 (66.2)
Patients with serious adverse events	209 (15.8)	114 (6.0)	323 (10.0)
Patients with severe adverse events	153 (11.6)	98 (5.1)	251 (7.8)
Patients discontinued due to adverse events	148 (11.2)	75 (3.9)	223 (6.9)
Patients with dose reduced or temporary discontinuation due to adverse events	353 (26.7)	259 (13.6)	612 (19.0)

BID=twice daily; pt-yr=patient-years.
Except for the total number of adverse events, patients are counted only once per treatment in each row.
MedDRA (v13.1) coding dictionary applied.
Includes Protocols A3921024 and A3921041.
Source: LTE Table 4.1.1 and Table 4.9.1 (pt-yr of drug exposure).

In the LTE studies, the incidence of TEAEs was higher in the 5 mg dose group for all SOCs compared to the 10 mg dose group (79.3% vs. 57.1%) but according to the applicant, this is due to a longer observation of patients treated with 5 mg BID. Actually, the incidence rate for all TEAEs, when calculated by exposure for event, was lower in the 5 mg dose group (47.3 new events/100 pt-yr) compared to the 10 mg dose group (124.9 new events/100 pt-yr).

Infections and infestations was the SOC with the highest number of AEs involving 1281 (39.7%) patients.

The phase 2 background MTX studies included 546 patients treated with different doses of tofacitinib (low dose, 5 mg BID, 10 mg BID, 15 mg BID and 20 mg QD) compared to placebo where 97 patients were included. The safety data from these phase 2 studies have shown that all severe events (37) occurred in tofacitinib groups and none with placebo. More patients experienced adverse events with study drug

(58.6%) than with placebo (49.5%). Particularly, more cases of infections have been observed in tofacitinib groups.

The phase 2 monotherapy studies included 736 patients treated with different doses of tofacitinib (low dose<5 mg BID, 5 mg BID, 10 mg BID, high dose >10 mg BID), 176 patients with placebo and 53 patients in adalimumab arm.

For the first 3 months of treatment, there were slightly more AE and SAE (53.9% and 2.6%) in all doses tofacitinib groups compared to active comparator (50.9% and 1.9%) and placebo (48.3% and 1.7%); 2.4% of severe AEs occurred with study drug while no severe adverse events were with adalimumab; more patients discontinued in adalimumab group (4-7.5%) compared to drug product (29-3.9%).

From 3 to 6 months: more AEs and SAEs in adalimumab group compared to all doses tofacitinib groups (45.5% and 6.8% vs. 26.3% and 2%) however based on only 44 patients treated with adalimumab and 297 patients treated with study product.

In the phase 2 studies, the event of herpes zoster occurred in 6 tofacitinib treated patients, 1 patient in placebo group and none with adalimumab.

In the high dose group (>10 mg BID) of tofacitinib, including 249 patients, the majority of patients (65.5%) had an AE, especially infections and blood and lymphatic system disorders (anaemia and leucopenia).

In the phase 3/LTE studies, weight increases have been frequently reported in the tofacitinib groups compared to placebo. Mean weight increase was approximately 2 kg by month 12.

Analysis of Adverse Events by Organ System or Syndrome

Infections, Including Herpes Zoster and Serious Infections

The most common serious infection reported in patients receiving tofacitinib was pneumonia; other commonly reported serious infections included skin and soft tissue infections. The incidence rate of serious infections was considerably higher than for placebo or active comparator (adalimumab) (see table 105).

Table 105 **Exposure Estimates and Incidence Rates for All Serious Infections in All Phase 3 and Long-Term Extension CP-690,550 Rheumatoid Arthritis Studies**

		CP-690,550					Adalimumab
Population		5 mg BID	10 mg BID	5 + 10 mg BID	All Doses	Placebo	40 mg SC q2w
P3 DMARD (0–12 months)	Total no. patients	973	969	1942	2435	559	204
	No. (%) patients with events	28 (2.9)	23 (2.4)	51 (2.6)	55 (2.3)	3 (0.5)	3 (1.5)
	Exposure for event (pt-yr)	784.34	795.29	1579.63	1836.01	174.53	178.66
	Incidence rate, in events per 100 pt-yr (95% CI)	3.570 (2.465, 5.170)	2.892 (1.922, 4.352)	3.229 (2.454, 4.248)	2.996 (2.300, 3.902)	1.719 (0.554, 5.330)	1.679 (0.542, 5.206)
P3 MONO (0–6 months)	Total no. patients	243	245	488	595	122	NA
	No. (%) patients with events	1 (0.4)	4 (1.6)	5 (1.0)	6 (1.0)	0	NA
	Exposure for event (pt-yr)	117.21	113.79	231.00	256.90	27.93	NA
	Incidence rate, in events per 100 pt-yr (95% CI)	0.853 (0.120, 6.057)	3.515 (1.319, 9.366)	2.165 (0.901, 5.200)	2.336 (1.049, 5.199)	0	NA (NA)
P3 ALL (0–12 months)	Total no. patients	1216	1214	2430	3030	681	204
	No. (%) patients with events	29 (2.4)	27 (2.2)	56 (2.3)	61 (2.0)	3 (0.4)	3 (1.5)
	Exposure for event (pt-yr)	900.87	909.08	1809.95	2093.80	202.46	178.66
	Incidence rate, in events per 100 pt-yr (95% CI)	3.217 (2.235, 4.629)	2.970 (2.037, 4.331)	3.093 (2.380, 4.019)	2.912 (2.266, 3.743)	1.482 (0.478, 4.594)	1.679 (0.542, 5.206)
LTE	Total no. patients	1321	1906	NA	3227	NA	NA
	No. (%) patients with events	50 (3.8)	43 (2.3)	NA	93 (2.9)	NA	NA
	Exposure for event (pt-yr)	2221.96	878.92	NA	3100.88	NA	NA
	Incidence rate, in events per 100 pt-yr (95% CI)	2.250 (1.706, 2.969)	4.892 (3.628, 6.597)	NA (NA)	2.999 (2.448, 3.675)	NA (NA)	NA (NA)

BID=twice a day; CI=confidence interval; LTE=long-term extension; NA=not applicable; IR=incidence rate; Pt=patient; q2w=every 2 weeks; SC=subcutaneous.
Includes all AEs reported on the Infection log page that were marked as serious in the project database.
The patients that are advanced from placebo to CP are counted in placebo until advancement and only in the CP All Doses group after advancement.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.
Includes Protocols A3921032, A3921044, A3921045, A3921046 and A3921064 (0-12 months); LTE: includes studies A3921024 and A3921041.
Source: P3DMARD Table s13.6.1, P3MONO Table s13.6.1, P3ALL Table s18.1 and LTE Table s18.1.

Patients experienced disseminated opportunistic infections including cryptococcal meningitis, disseminated TB, Pneumocystis jiroveci pneumonias and CMV viraemias. The patients who develop opportunistic infections/TB appear not to recover with large numbers of “unresolved” events in the line listings. These cases occurred with both doses of study drug, 12 cases with 5 mg BID and 15 cases with 10 mg BID.

Early signals of the drug’s ability to significantly impair the cellular immune response was identified in the P2 studies with decreases in NK cells at the proposed posology of the 5/10 mg dose and in the monkey studies with significant decreases in CD4/8 counts at levels of human exposure. Furthermore there is evidence of irreversibility of the pharmacodynamic effect on NK cells in monkeys.

Nine (9) deaths in the tofacitinib groups during the tofacitinib development programme (phase 2, 3 and LTE studies) have been linked to infections, including 8 deaths due to pneumonia; 3 additional deaths were recorded to infections. Six deaths occurred with 5 mg BID, one with 3 mg BID and two with 10 mg BID. One death has been observed in placebo group and no deaths occurred in active comparator group.

The incidence rate of herpes zoster is higher in study drug groups compared to placebo and adalimumab (3% in all dose group, 0.4% in placebo group and 2.5% in adalimumab group in phase 3 all studies 0-12 months) and was not dose-related: 3.2% and 3.1% in 5 mg BID and 10 mg BID groups.

In long term extension studies, 134 out of 3227 patients (4.2%) experienced herpes zoster infection. The incidence rate was greater in elderly >65 years, especially during the extension. One case of disseminated, multidermatomal herpes zoster is noted. Overall, there were 16 cases of serious herpes zoster.

Twelve cases of tuberculosis occurred, 3 cases in the 5 mg dose group and 8 in the 10 mg dose group, and 1 was initially on 5 mg BID and later switched to 10 mg BID while no cases occurred with placebo or adalimumab.

The risk of opportunistic infections was high in patients treated with tofacitinib including 27 cases in the phase 3 and LTE studies while no cases were reported in the placebo and adalimumab groups.

The risk of opportunistic infections seemed to be maximal in first 90 days of exposure, increasing also with the age.

Malignancies, including Lymphomas/Lymphoproliferative Disorders

There were 65 malignancies in total, including 15 additional cases for 6-month updated period of studies while no cases occurred with placebo; 3 cases were observed in adalimumab group. Additional 15 cases were not described in the submitted response document. The exposure period was very short for comparative groups; the calculation of the overall malignancy incidence rate showed that IR was significantly increased with tofacitinib in comparison with placebo. In particular, incidence rates over treatment duration with tofacitinib increased between 2nd and 3rd year of treatment (1.93 and 1.60).

The incidence rate of adalimumab was 1.58, and the IR of in the overall RA programme was 0.56 (inferior to tofacitinib).

Lung cancer was the most common malignancy, followed by breast cancer and lymphomas. The incidence of malignancies is higher in long-term extension studies. Higher rate is found in older population, as expected.

There were 12 deaths due to malignancies.

Table 106 Incidence Rates of Malignancies (Excluding Non-melanoma Skin Cancer): Overall (0-12 Months) in Phase 2, Phase 3, and Long-Term Extension Studies

Population		CP-690,550 Dose Group (BID)				Pbo	ADA
		5 mg	10 mg	5 + 10 mg	All Doses		
P2P3LTE	Total no. patients	-	-	-	4789	-	-
	No. (%) patients with events	-	-	-	50 (1.0)	-	-
	Exposure for event (pt-yr)	-	-	-	5648.43	-	-
	Incidence rate, in events per 100 pt-yr (95% CI)	-	-	-	0.885 (0.671, 1.168)	-	-
P3ALL	Total no. patients	1216	1214	2430	3030	681	204
	No. (%) patients with events	5 (0.4)	8 (0.7)	13 (0.5)	13 (0.4)	-	1 (0.5)
	Exposure for event (pt-yr)	903.50	910.24	1813.74	2097.84	202.55	178.09
	Incidence rate, in events per 100 pt-yr (95% CI)	0.553 (0.230, 1.330)	0.879 (0.440, 1.757)	0.717 (0.416, 1.234)	0.620 (0.360, 1.067)	0	0.559 (0.079, 3.968)
LTE	Total no. patients	1321	1906	-	3227	-	-
	No. (%) patients with events	23 (1.7)	12 (0.6)	-	35 (1.1)	-	-
	Exposure for event (pt-yr)	2235.13	881.39	-	3116.51	-	-
	Incidence rate, in events per 100 pt-yr (95% CI)	1.029 (0.684, 1.549)	1.361 (0.773, 2.397)	-	1.123 (0.806, 1.564)	-	-

ADA=adalimumab; BID=twice daily; CI=confidence interval; LTE=long-term extension studies; P2P3LTE=Phase 2 and 3 and long-term extension studies; P3ALL= Phase 3 studies; Pbo=placebo; pt-yr=patient-years.
Cases based on safety database.
Some events may have occurred after the end of treatment; these events were counted in the numerator and patients' full treatment exposure was included in denominator.
P3ALL: The patients that are advanced from placebo to CP are counted in placebo until advancement and only in the CP All doses group after advancement. Includes Protocols A3921032, A3921044(1 year), A3921045, A3921046 and A3921064
Source: P2P3LTE Table 71.4a; P3ALL Table s16.1.7a; LTE Table s16.1.7a.

Three (3) lymphomas were observed in tofacitinib groups (one in the phase 3, 2 in the LTE studies) while there were no cases in the placebo or adalimumab groups. One B-cell lymphoma, one Hodgkin's lymphoma are mentioned in the summary list.

In the all phase 3 studies, 8 cases of non-melanoma skin cancer were reported, including 5 cases in the 10 mg dose group. Additional 14 cases have been observed in the LTE studies, 8 in the 5 mg dose and 6 in the 10 mg dose group.

With regards to the updated data on malignancies, patients with RA treated with tofacitinib were at a higher risk than those treated with placebo. The incidence of malignancies was higher in long-term extension studies.

Lipid Increases and the Potential for Cardiovascular Risk

Lipids: important dose-dependent increases in LDL-c, HDL-c and total cholesterol levels (14.2%, 15.5%, 12.7% with 5mg and 19.6%, 17.6%, 17.1% with 10 mg) have been shown within 3 months of initiating therapy and remained increased thereafter. With atorvastatine, significant LDL-c reduction was observed.

Dyslipidemia has been reported as adverse event more frequently in tofacitinib groups (76, 3.1%) than in the placebo group (8, 1.2%). There were no serious events but 1 permanent discontinuation due to dyslipidemia has been observed.

Hypertension: in the all Phase 3 studies, a small but significant increase in DBP has been observed in patients with study treatment. In addition, the modelling analysis of the dose-response relationship from the Phase 2 data showed a small and statistically significant difference in mean SBP over placebo (0.3 and 0.6 mm Hg for the 5 mg dose and the 10 mg dose, respectively) without significant differences in mean DBP (approximately 0.3 mm Hg for the 10 mg dose). The clinical relevance of these findings in the context of CV risk at long term is unknown. More AE of hypertension have been reported in the 5 mg dose and the 10 mg dose groups compared to placebo (2.1%, 2.9% vs. 1.5% for the first 3 months). In the controlled study 1064, AE of hypertension occurred in 1% and 3% of patients in 5 mg and 10 mg groups, respectively compared to 1.9% in placebo and 0% in adalimumab group.

Two deaths due to hypertension are also to be noted.

Cardiovascular risk including blood pressure changes, lipid changes and CV event rate, was assessed by an independent safety committee (CV SEAC) of 3 cardiology specialists for the phase 3 studies. The baseline CV profile risk, based on the Framingham score was comparable between all groups of treatment. CV SEAC performed the adjudication of CV events: death (CV and non-CV) and non-fatal CV events like myocardial infarction, coronary revascularisation, congestive heart failure (CHF), cerebrovascular events, peripheral vascular disease and hospitalisation for unstable angina. A blinded fashion was used.

The incidence of major CV events, fatal and non-fatal and non-fatal MI was lower for study drug than for adalimumab (0.572, 0.095, 0.191 vs. 1.677, 0.559, 1.118). The incidence of MACE and non-fatal cerebrovascular accidents was also lower in study drug groups compared to placebo 0.334 vs. 0.988).

However, the incidence of CHF was higher in study drug group (0.286) compared to adalimumab and placebo (no events). All CHF cases occurred in 10 mg BID group. Small number of patients in adalimumab (204) and placebo group (681) with large 95% CI should be taken into account when analyse these data. It is agreed that as events were more balanced in the LTE studies between the 5 mg dose and the 10 mg dose the dose-related differences observed initially observed in the P3 trials are likely to be due to chance.

Gastrointestinal Perforation Adverse events

Cases of GI perforations were adjudicated by 2 gastroenterologists. A short assessment of all 19 adjudicated cases has been provided. In total, 10 cases (including 1 death) were adjudicated as definite or probable GI perforation (incidence rate 0.177) while no cases were reported with adalimumab or placebo. GI perforation was primarily of lower GI tract but there was also one case of upper GI tract and cases of not specified locations.

GI perforations occurred with the high dose of 10 mg BID but also with 5 mg BID (2 definite and 2 probable cases); one definite case occurred with a dose of 3 mg. No events were observed with placebo or adalimumab.

Two (2) cases reported death as an outcome but one case of death was probably due to GI perforation (one patient in the 5 mg dose group had GI perforation of lower GI tract due to appendicitis and sepsis with necrosis of ascending colon; he died on day 664). The other case was mentioned as malignant ascites due to ovarian cancer/peritoneal carcinomatosis and was adjudicated as not related to GI perforation.

Hematologic events

Percentages of patients with mild to moderate decreases in haemoglobin in tofacitinib treatment groups (2.9% for the 5 mg dose, 4.8% for the 10 mg dose) were comparable to those for placebo (4.0%). No cases were reported with adalimumab. In the phase 3 studies, 3 SAEs of anaemia were observed in the 10 mg dose group and 5 discontinuations were noted. In the LTE studies, 5 events of anaemia were severe; 5 discontinuations were due to anaemia.

Overall in the all phase 3/LTE studies, 28 patients had potentially life threatening decreases in haemoglobin.

A dose-dependent neutropenia was observed in RA patients treated with study drug compared to placebo. The percentage of patients with mild confirmed neutropenia was somewhat dose dependent: 1.5% for the 5 mg dose and 2.0% for the 10 mg dose compared with 1.0% for placebo. Cases were also observed in the adalimumab-treated patients, but the number of patients was small. There were no potential life-threatening neutropenia.

Increased incidence of lymphopenia has been observed with tofacitinib compared to placebo and active comparator arm in the phase 3 studies. In the LTE studies, mean decreases were still observed.

The AEs of lymphopenia was observed in 11 (0.9%) and 20 (1.6%) patients in the 5 and the 10 mg dose groups, respectively, compared with 2 (0.3%) for placebo in the Phase 3 studies. Nine discontinuations occurred with study drug and one with adalimumab.

In the LTE studies, 54 (4.1%) and 31 (1.6%) of patients in the tofacitinib 5 and the 10 mg dose groups, respectively, experienced leucopenia; 3 AEs were severe and one EI was serious. Five (5) discontinuations occurred with study drug. Ten (10) patients had confirmed life-threatening lymphopenia associated with treated infection.

Increased transaminases

In the phase 3 studies, cases of hepatic enzymes increased were commonly reported: in background DMARD studies, first 3 months: 28 ALT, 20 AST increased with tofacitinib, 1 in adalimumab group, 11 with placebo.

A rate of hepatic disorder AEs was slightly higher in the tofacitinib 5 and the 10 mg dose groups (1.8% and 2.5%, respectively) compared with the placebo group (0.5%) and the adalimumab group (1.5%) from 3 to 6 month. After 6 months of treatment, more patients had hepatic AEs in the tofacitinib 5 and the 10 mg dose groups (2.4% and 3.3%, respectively) than in the adalimumab group (0.5%).

In the LTE studies, in total, 163/3227 (5.1%) patients with hepatic disorders were observed; 10 (0.3%) SAE; 23 (0.7%) of discontinuations; 18 hepatic steatosis were reported; 54 ALT increased, 40 AST increased, 1 bilirubin increased, 22 GGT increased; in addition, 28 hepatic enzyme increased.

The incidence rates of >3xULN ALT elevation (including 5xULN and 10x ULN) is greater than with adalimumab Marked ALT elevation of 5x, 10x, or 20x ULN in modest numbers of subjects as compared to the control group has a high sensitivity for the prediction of DILI although specificity is sub-optimum. In addition, given the findings in one subject of biochemical abnormalities that met the criteria for Hy's law with no definitive alternative causation, the potential for tofacitinib to cause DILI cannot be ruled out. The observation that the biochemical test values worsened following discontinuation does not exclude this as representing a case of DILI.

Creatinine and Renal Disorders

Small mean increases in creatinine levels were observed in Phase 3/LTE studies, greater in the tofacitinib 10 mg dose group:

- TEAE 0.3%, 0.6%, 0.1%, and 1.0% for the tofacitinib 5 mg dose, the 10 mg dose, placebo, and adalimumab groups, respectively.
- 41 patients with acute renal failure in phase3/LTE studies with tofacitinib (19 patients in the tofacitinib 5 mg dose, 22 in the tofacitinib 10 mg dose group), 2 with placebo; 13 SAEs; 20 permanent discontinuations with tofacitinib, 2 with placebo.
- Seven patients with acute renal failure died.

Creatine Kinase and Myopathy

Creatine kinase levels were not monitored in phase 2 studies.

In the phase 3 studies, dose-dependent increase of CPK levels has been commonly observed in tofacitinib groups: from 70 IU/L at baseline to 129 IU/L at 12 months.

The percentage of AEs was higher for study drug: 0.7%, 2.1%, 0.4%, and 0.5% for the tofacitinib 5 mg dose, the tofacitinib 10 mg dose, placebo, and adalimumab groups, respectively.

In the LTE studies, 27 (2.0%) and 19 (1.0%) patients were reported to have an AE of blood creatine phosphokinase increased.

Six (6) discontinuations for CPK increased were reported in the phase 3/LTE studies.

In addition, cases of rhabdomyolysis have been reported in tofacitinib groups of treatment.

- One (1) case was reported in a one patient in the Phase 3 studies on D357; this patient suffered also from moderate renal failure, increased CK levels, severe CHF and severe pulmonary hypertension; he died on D374 due to respiratory failure.
- One (1) SAE of rhabdomyolysis was observed in the renal transplant Study 1030 in one patient who received 5 doses of tofacitinib15 following kidney transplantation; 3 days after transplantation, patient developed fulminant rhabdomyolysis with large increases in CK (88500 IU/L to >100,000 IU/L).

The applicant assessed whether there was any impact of atorvastatin on creatine kinase levels in study 1109. The study was of 12 weeks duration only, which may not be long enough to capture any pharmacodynamic interaction of the two drugs on CK levels and the potential to increase the risk of rhabdomyolysis. A total of 8 patients in the P3 ALL studies were reported to have a treatment-emergent AE coding to the SMQ of Rhabdomyolysis/Myopathy within (±) 7 days of a CK value ≥5 × ULN but without adverse event. One case was due to atorvastatine.

In the LTE studies, 10 additional patients reported an AE coded to the SMQ of rhabdomyolysis/myopathy.

Demyelinating Disorders

No events were reported that coded to the MedDRA PT of progressive multifocal leukoencephalopathy or the HLGT of demyelinating disorders.

Interstitial Lung Disease

The ILD incidence rates for the LTE studies, as of 29 September 2011 are provided in table 107.

Table 107 **Exposure Estimates and Incidence Rates for Interstitial Lung Disease in Long-Term Extension Studies (All Patients), as of 29 September 2011**

	CP-690,550		
	5 mg BID	10 mg BID	All Doses
Total no. patients	1370	2145	3515
No. patients with AEs (%)	1 (0.07)	6 (0.28)	7 (0.20)
Exposure for event (pt-yr)	2725.8	1682.6	4408.5
Incidence rate, in events/100 pt-yr (95% CI)	0.037 (0.005, 0.260)	0.357 (0.160, 0.794)	0.159 (0.076, 0.333)

Data as of 29 September 2011
BID=twice daily, CI=confidence interval, pt-yr=patient-years.
Some events may have occurred after the end of treatment, these events were counted in the numerator and patients' full treatment exposure was included in denominator.
Includes Protocols A3921024 and A3921041.
Source: SCS 4MSU LTE Table s28.1 (replaced)

A tabular summary of ILD adjudication was provided by the applicant analysing 24 cases of individual cases of possible or probable ILD. Among these cases, 13 cases had an alternative diagnosis and 11 were considered as ILD, including one case of progressive ILD leading to death. In all 11 cases of ILD, patients were treated with other RA therapies. However, the role of tofacitinib in exacerbation of the disease cannot be excluded. No cases have been observed with adalimumab and one case occurred with placebo.

Serious adverse event / deaths / other significant events

Deaths

In total, 34 deaths occurred in tofacitinib-treated patients, 12 in all phase 3 studies and 20 in the LTE studies. The incidence rates were calculated for all phase 3 comparative studies versus placebo (1 death) and adalimumab (1 death). With regards to all deaths, incidence rate was slightly higher with tofacitinib compared to placebo (0.572 events/100 pt-yr vs. 0.494) and similar with adalimumab (0.559). However, the exposure to placebo and adalimumab was significantly lower (10-fold less than with tofacitinib) to generate meaningful results. Furthermore, the confidence interval (95% CI) for placebo and adalimumab was large compared to tofacitinib preventing firm conclusions. Regarding LTE studies, the incidence rate for tofacitinib was 0.641 but no comparative data are available.

Safety data on fatal events were updated extending this period until 29 September 2011. In total, 42 deaths occurred in tofacitinib-treated patients. Eight additional deaths, all in the LTE studies, have been reported with tofacitinib (3 with 5mg BID and 5 with 10 mg BID): 4 were considered as related to study drug by the investigators (sepsis/pneumonia, synovial sarcoma with pulmonary metastases, lung neoplasm, lung adenocarcinoma) and 4 as not related to study drug (gallbladder cancer, small cell lung cancer metastatic, pneumonia, cardio-respiratory arrest). Concerning cases of death considered as not related to study drug, the role of tofacitinib cannot be excluded in cases of cancer and pneumonia. In addition, a female patient with RA and multiple co-morbidities who suffered cardio-respiratory arrest developed pneumonia one week before she died; the imputability of tofacitinib in the development of infection cannot be excluded.

Two (2) additional deaths with adalimumab (severe medullary hypoplasia, NSC lung adenocarcinoma) occurred in the comparative study 1064, more than 200 days after drug discontinuation. A case of death due to hypoplastic marrow was related to adalimumab.

However, the exposure to placebo and adalimumab was significantly lower and their confidence interval (95% CI) was large compared to tofacitinib. In so far as the comparative data are very limited, almost all deaths occurred with tofacitinib.

Serious Adverse Events

In the phase 3 studies, treatment-emergent SAEs were reported in 3.1% and 2.7% of patients in the tofacitinib 5 mg dose and the tofacitinib 10 mg dose groups, respectively and in 3.5% of patients in the placebo group during the first 3 months of the studies and similarly from months 3 to 6. During Months >6, SAEs were reported for 3.7% of patients in the tofacitinib groups.

The incidence rates of SAEs in the tofacitinib 5 mg dose and the tofacitinib 10 mg dose groups were estimated to be 11.867 and 9.758 events per 100 pt-yr, respectively, compared with 15.024 and 10.868 events per 100 pt-yr for placebo and adalimumab, respectively for the 12 months.

In the LTE studies, approximately 16% of patients in the tofacitinib 5 mg dose group reported treatment-emergent SAEs of all causality and 6% in the tofacitinib 10 mg dose group (but the exposure was longer in the tofacitinib 5 mg dose group).

In total, there were 8 cases of herpes zoster, 23 pneumonia, 8 UTI, 7 cholelithiasis, 6 cellulitis, 50 cancer in 3227 patients in total.

During the phase 2 studies, the CHMP noted 2 cases of herpes zoster and 2 of pneumonia, none in placebo or adalimumab groups.

Laboratory findings

Haematology

In the phase 3 studies, an increase in the number of patients with haemoglobin decreases over time up to 12 month was noted, especially in the tofacitinib 10 mg dose group and in the placebo to the tofacitinib 10 mg dose group where 10.7% and 9.8% of patients had mild to moderate haemoglobin decrease, respectively, compared to 4.9% in adalimumab group. Haemoglobin decrease was confirmed in LTE studies with 12.4 and 8.2% of mild to moderate and 2.8% and 1.1% of severe decrease in the tofacitinib 5 and the 10 mg dose groups, respectively.

Overall in the all phase 3 studies, up to 12 months, 5 patients had potentially life threatening decreases in haemoglobin: 1 patient in the tofacitinib 10 mg dose group, 1 in placebo to the tofacitinib 5 mg dose group and 3 patients in the placebo to the tofacitinib 10 mg dose group. In the LTE studies, 23 patients were with potential life threatening decreases in haemoglobin.

Neutrophils/Lymphocytes

In the phase 3 studies, a decrease in neutrophil counts was higher in tofacitinib groups than with placebo. In the LTE studies, mean decrease was still observed. However, no cases of potential life threatening neutropenia were reported.

Of note, after an initial increase in lymphocyte levels in tofacitinib groups and adalimumab group, the lymphocyte decrease in tofacitinib groups occurred continuously through 12 months in the phase 3 studies, whereas the lymphocyte increase persisted in adalimumab group.

High rate of mild confirmed lymphopenia (24.1% and 25.6% in the tofacitinib 5 and the 10 mg dose groups, respectively) and even higher rate of moderate to severe lymphopenia (58.6% and 31.1% in the 5 and the 10 mg dose groups, respectively) in the long term studies are of concern. Furthermore, 10 patients had potentially life threatening due to lymphopenia.

Platelets

Mean decreases in platelet have been observed in tofacitinib groups but remained within the normal ranges.

Serum creatinine

Mean increases in creatinine levels have been observed in tofacitinib groups in the phase 3/LTE studies, greater in the tofacitinib 10 mg dose group.

Creatine kinase

Mean increases in creatin kinase levels have been frequently observed with tofacitinib in the phase 3/LTE studies.

Safety in special populations

Intrinsic factors

- Age: In the phase 3 studies, the data provided by applicant shows that the percentages of elderly patients (<65, 65-74, 75-84, and ≥85 years) who experienced an SAE with tofacitinib 5 mg BID are increased: 2.5; 6.4; 9.4; 100. The incidence rate of infections and infestations also increased with age in the tofacitinib 5 mg BID group (19.4; 21.7; 31.3). For the same age groups the incidence rate of infections with adalimumab 5 mg BID was lower: 16.1; 17.9; 0.

In the LTE studies the percentages of patients who experienced an SAE with tofacitinib 5 mg BID is increased: 15.1; 31.5; 43.5. For the same age groups the incidence rate of CNS disorders with tofacitinib 5 mg BID was 14.8; 22.5; 30.4.

Provided data demonstrated that an increase of AE in elderly patients, particularly the percentages of SAE, with tofacitinib cannot be excluded.

- Gender: overall, there did not appear to be any trends by sex in the AEs, SAEs and AEs leading to discontinuation that were consistent over time. Of note, there were approximately 5 times as many women as men in the Phase 3 studies, which limits the ability to draw conclusions.

Overall mortality was higher in men than in women who received tofacitinib: 1.4% and 1.5% of men died after the start of the Phase 3 and LTE studies, respectively, compared with 0.2% and 0.4% of women, respectively.

Men experienced increased rates of several specific events compared with women, including serious infections, TB, lung cancer, and NMSC. Women experienced increased rates of herpes zoster compared with men.

- **Race**: no pattern for a different safety profile with regard to race was apparent for tofacitinib treatment groups relative to the other treatment groups. There were numerically higher percentages of black patients in several AE subset categories for the tofacitinib treatment groups; however, this pattern was also seen for placebo and adalimumab in the first 3 months and is confounded by the small number of black patients in each treatment group.

Asian patients exposed to tofacitinib had a higher incidence rate of herpes zoster than did patients of other races. Two (2) of 3 cases of *P jiroveci* pneumonia and all 3 cases of gastric cancer occurred in patients in Japan, which has a notably higher rate of both events compared with other countries.

Asian patients experienced slightly increased event rates of AEs coding to the SMQ of Drug-induced hepatic disorder compared with patients of non-Asian race.

Extrinsic factors

- Overdose: tofacitinib has been administered in Phase 1 studies in doses as high as 100 mg in a single dose to healthy subjects (Studies 1002 and 1028) and 50 mg BID for 14 days to healthy subjects with psoriasis (Study 1003). Doses up to 30 mg BID have been given in a Phase 2 RA monotherapy study for 6 weeks (Study A3921019).

No overdoses were reported in Phase 1 or 2 studies. “Overdose” was reported as an AE in Phase 3 studies for 5 patients receiving tofacitinib (3 in the tofacitinib 5 mg dose group, 1 in the tofacitinib 10 mg dose group, and 1 in the placebo to the 10 mg dose sequence); an overdose was reported for 1 patient receiving the 10 mg dose in the LTE studies. No AEs of overdose were serious and all were considered to be mild or moderate in severity. In only one case of overdose was a concurrent AE reported (nightmares). In half of the cases of overdose, the patients were assigned to the tofacitinib 5 mg dose and took no more than the equivalent of the tofacitinib 10 mg dose (total daily dose of 20 mg).

- Drug abuse: There were no reports of drug abuse or dependence or other information relevant to the potential for drug abuse in these studies.

- Withdrawal and rebound: There were no reports of withdrawal or rebound effects in any of these studies.

- Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability: there were no reports of impairment of the senses, coordination, or other factors that would result in diminished ability to drive a vehicle or operate machinery or would impair mental ability.

- Pregnancy, lactation and fertility

There is very limited clinical experience and no relevant information can be drawn from pregnancy outcomes during clinical trials. The applicant was requested to reconsider the level of recommendation in

pregnancy as stated in the guideline EMEA/CHMP/203927/2005. The applicant proposed to mention in the product information, that tofacitinib should not be used during pregnancy unless clearly necessary and women of childbearing potential must use effective contraception during treatment and for at least 28 days after stopping treatment with tofacitinib.

Immunological events

There are major concerns in relation to lymphopaenias and immuno-suppression caused by tofacitinib resulting in serious and opportunistic infections. These are discussed in the safety section under infections. Other immunological events analysed by the applicant did not raise particular concern, however autoimmune diseases as well as severe skin reactions should be monitored and analysed in the clinical trials.

Discontinuation due to adverse events

When compared to placebo and adalimumab, similar percentage of patients discontinued from studies for any reason: 401 (20.6%) in tofacitinib groups (equal number between two doses), 106 (19%) in placebo and 42 (20.6%) in adalimumab group. The most common reason for discontinuation from study was adverse event. More discontinuations for an AE related to study drug were reported in tofacitinib groups (129 patients-6.6%) and with adalimumab (16 pts-7.8%) than with placebo (16 pts-2.9%). Few patients were lost to follow up: 13 in tofacitinib groups, 6 in placebo group, none in adalimumab group.

Up to 3 months, most patients (24-1.2%) discontinued due to infections, including 4 herpes zoster; 6 cases of skin and subcutaneous tissue disorders have been reported, 5 cases of AST/ALT increased etc.

In the LTE studies, 441 (13.7%) patients discontinued from studies for any reason in tofacitinib groups: 302 (22.9%) in the tofacitinib 5 mg dose and 139 (7.3%) in the tofacitinib 10 mg dose group. The most common reason for discontinuation from study was adverse event, in 144 (4.5%) patients.

Table 108 **Discontinuations From Study for Any Reason in Phase 3 DMARD Studies: Number (%) of Patients (0 to 12 Months)**

	CP-690,550				
Reason	5 mg BID n=973	10 mg BID n=969	All Doses n=1942	Placebo n=559	Adalimumab n=204
Any reason	206 (21.2)	195 (20.1)	401 (20.6)	106 (19.0)	42 (20.6)
Patient died	1 (0.1)	3 (0.3)	4 (0.2)	1 (0.2)	1 (0.5)
Adverse event					
Related to study drug	68 (7.0)	61 (6.3)	129 (6.6)	16 (2.9)	16 (7.8)
Not related to study drug	25 (2.6)	34 (3.5)	59 (3.0)	15 (2.7)	6 (2.9)
Lack of efficacy	31 (3.2)	27 (2.8)	58 (3.0)	27 (4.8)	6 (2.9)
Lost to follow up	9 (0.9)	4 (0.4)	13 (0.7)	6 (1.1)	0
Patient no longer willing to participate in study	29 (3.0)	23 (2.4)	52 (2.7)	9 (1.6)	1(0.5)
Other	43 (4.4)	43 (4.4)	86 (4.4)	32 (5.7)	12 (5.9)

BID=twice daily.
Patients reassigned at Month 3 or at Month 6 from placebo to CP-690,550 5 mg BID treatment or to CP-690,550 10 mg BID treatment are included in their respective reassigned treatment group.
Adalimumab treatment is only in Study A3921064.
Includes Protocols A3921032, A3921044 (up to 12 months), A3921046 and A3921064.
Source: P3DMARD Table 8.1.1.

2.6.1. Discussion on clinical safety

Overall, 4816 patients (cut-off date 29th March 2011) were included in the clinical part of the development programme across all treatment groups of patients with rheumatoid arthritis. The safety summary focused on the safety data that were pooled for 5 phase 3 studies (4 background DMARD studies: 1032, 1044, 1046, 1064 and one monotherapy study: 1045) and 2 long-term extension, open-label studies in patients initially enrolled in phase 2 or 3 DB studies (phase 2B 1024, phase 3

1041).

A summary of the one-year analysis report of the tofacitinib monotherapy versus methotrexate study A3921069 was provided. These results showed that tofacitinib safety profile in this study is similar to the safety profile seen in previous studies with tofacitinib, confirming the unfavourable risks of tofacitinib:

- SAEs of infectious type were more frequent in the tofacitinib groups than in the MTX group, particularly pneumonia (3 vs. 0) and herpes zoster (2 vs. 0). In addition, 1 patient in the tofacitinib 10 mg BID group experienced bone tuberculosis.
- AE leading to treatment discontinuation: blood creatinine increased in 5 patients in the tofacitinib groups vs. 0 in the MTX group, rheumatoid arthritis in 3 patients in the tofacitinib groups vs. 0 in the MTX group, blood creatine phosphokinase increased in 2 patients in the tofacitinib group vs. 0 in the MTX group, herpes zoster in 2 patients in the tofacitinib groups vs. 0 in the MTX group and transaminases increase in 2 patients in the tofacitinib group vs. 0 in the MTX group.

The following AEs were reported at least 3 times as often in patients treated with tofacitinib vs. MTX: bronchitis, gamma-glutamyltransferase increased, weight increase and hypercholesterolemia. Patients receiving tofacitinib at the 10 mg BID dose experienced 2 times more frequently abdominal pain, blood creatinine phosphate increased and rash. Regarding laboratory values, patients in the tofacitinib groups showed higher proportions of patients with mild, moderate or severe neutropenia. 5 patients had AEs of thrombocytopenia, all in the tofacitinib groups. More patients in the 10 mg BID tofacitinib groups showed increased of baseline creatinine value. Increases in mean total cholesterol, HDL, LDL apolipopoprotein A-1 and b-100 concentrations were also reported in the tofacitinib groups. More patients (around x3) in the tofacitinib groups experienced hypertension or blood pressure increased than in the MTX group.

Five phase 3 studies were placebo-controlled; one of these studies included active comparator arm (adalimumab) involving only patients.

Limited safety data of tofacitinib in other indications (plaque psoriasis, renal transplantation, Crohn's disease, and ulcerative colitis) correspond to those reported in the RA studies and confirm the immunosuppressive nature of the drug.

Long-term safety data: a total of 3822 patients received a study product for at least 6 months, 2951 patients received at least 1 year of treatment, and 693 patients received at least 2 years of the tofacitinib 5 mg dose or the tofacitinib 10 mg dose treatment. Five patients were treated for 4 years.

Adverse events: the number of patients with AE, with SAEs or discontinuations was comparable between the study drug (5 and 10 mg BID) and placebo or adalimumab up to 3 months; between 3 and 6 months, the number of AEs increased in study drug groups (39.7% and 37.5% for 5 and 10 mg BID) compared to placebo (26.2%) and adalimumab (33.3%) with more temporary discontinuations due to AEs (7.5% and 6.6% for 5 and 10 mg BID groups vs. 1.8% and 4.9% for placebo and adalimumab), seen also after 6 months of treatment.

Major safety issues:

Infections*:* The risk of infection is higher in patients treated with tofacitinib compared to placebo and adalimumab. Patients developed serious and fatal opportunistic infections including cryptococcal meningitis and *Pneumocystis jirovecii* pneumonia. Opportunistic infections occurred only with tofacitinib. There was also a high incidence of TB including disseminated TB in areas of high geographic prevalence despit TB screening and use of isoniazid for treatment of latent TB. All these events are suggestive of impaired cell-mediated immunity. The additional data provided by the applicant confirmed a decrease from baseline for CD3/4/8/56 cells with an increase in CD19 cells

with tofacitinib use. This decrease persists to month 22 for CD4 and CD8 cells, however returns to baseline for CD56 cells by month 22. The response data confirmed evidence of exposure-related increased incidence of serious and treated infections. The exposure-response data did not confirm any trends for dose and the risk of opportunistic infections. The identification of trends related to T-cell subset analysis and infection was limited as despite the non-clinical studies indicating dose-related T-cell subset decreases, the applicant did not collect WBC sub-set data in the P3 studies. The applicant's proposed strategy to attempt to reduce the risk of opportunistic infections using a cut-off for total lymphocyte cell counts of 500 cells/mm^3 is not endorsed by the CHMP. It is noted that there is some evidence of a higher rate of serious infections in patients with a confirmed ALC of <500 cells/mm^3, however there is not currently sufficient data to demonstrate whether dose reduction and/or treatment suspension and/or discontinuation for patients with a confirmed ALC of <500 cells/mm^3 would be appropriate or adequate to minimise the risk of serious and opportunistic infections in these patients. Further data would be required to demonstrate the appropriateness of this proposed measure.

- *Tuberculosis*: One of the main exclusion criteria during the development programme of tofacitinib was active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB). However, 225 patients with latent TB infection were allowed to enrol in the Phase 3 studies after receiving approximately 1 month of isoniazid therapy; none of these patients developed an active TB infection. Nevertheless, cases of TB occurred during the studies in tofacitinib treatment groups. Overall, 12 cases of tuberculosis have been reported in patients treated with both doses of tofacitinib while no cases occurred with placebo or adalimumab. A high incidence of TB occurred despite the incorporation of TB screening and in the development programme. The presence of extra-pulmonary dissemination is again suggestive of impaired cell-mediated immunity.

- *Neutropenia/lymphopenia*: Tofacitinib treatment was associated with an increased incidence of neutropenia and lymphopenia compared to placebo and adalimumab in phase 3 studies. The incidence of potentially life-threatening lymphopaenias associated with serious or treated infections in extremely high (40% and 80% respectively). No episodes of life-threatening lymphopaenia occurred with use of adalimumab. The spectrum of observed infections associated with the lymphopaenias could have been predicted from the mechanism of action of tofacitinib and the consequential severe impairment of cell-mediated immunity. The applicant has not presented adequate evidence of reversibility of this pharmacodynamic effect on the immune system.

- *Herpes zoster*: the incidence rate of herpes zoster was higher in study drug groups compared to placebo and adalimumab in the phase 3 studies. In the long term extension studies, 134 out of 3227 patients (4.2%) experienced herpes zoster infection. Asian race was a predictor of herpes zoster infection. The applicant has proposed to include this risk in Asian patients in the RMP and the product information

- ***Malignancies/lymphoma***: patients with RA treated with tofacitinib (65 malignancies excluding non-melanoma skin cancer and 26 NMSC) were at a higher risk of malignancies than those treated with adalimumab (3 cases) or placebo (no cases). The incidence of malignancies was higher in long-term extension studies, in particular with ***rates increased betw***een 2nd and 3rd year of treatment.

Interstitial lung disease (ILD): There is a x10 fold increase in the incidence of ILD when the incidence rates at 5 mg is compared with 10 mg. In addition, there is clustering ^wi^th mor^e^ incidences observed in Asian patients, the reasons are unclear.

Creatinine levels and Acute renal failure: The etiology was often unclear, or related to different

pathologies: infections, sepsis, dehydration, shock. Concomitant medications were usual. A review of SAEs related to renal function was provided by the applicant and in most cases of acute renal failure, the cause was pre-renal and not related to study drug.

Creatine kinase levels and rhabdomyolysis: there is an issue of blood CK levels increase that has been frequently observed with tofacitinib. Two cases of rhabdomyolysis, including one deathhave been reported in tofacitinib groups of treatment. Lastly, 18 patients (9 in the tofacitinib5 mg dose, 9 in the tofacitinib 10 mg dose) in the P3ALL/LTE studies were reported to have a treatment-emergent AE coding to the SMQ of Rhabdomyolysis/Myopathy within (±)7 days of a CK value ≥5 × ULN included one case due to atorvastatin. The concomitant use of statins known to cause the elevation of CK is questionable. The data on reported cases are not reassuring with regards to the risk of rhabdomyolysis but can be manageable according to the updated RMP and risk minimisation measures proposed by the applicant.

Lipids levels and CV risk: significant increases in lipids levels are of concern with regards to the potential cardiovascular risk, especially with long-term treatment of tofacitinib. Important dose-dependent increases in LDL-c, HDL-c and total cholesterol levels (14.2%, 15.5%, 12.7% with 5mg and 19.6%, 17.6%, 17.1% with 10 mg) have been shown within 3 months of initiating therapy and remained increased thereafter whereas no changes have been observed with placebo and adalimumab. More cases of congestive heart failure have been reported with study drug compared to placebo as well as hypertension. Given that RA is associated with increased rates of cardiovascular illness (MI, cerebrovascular events, heart failure), these data are not reassuring. In LTE studies, the incidence of all CV events was lower than in phase 3 studies, but the period is too short to draw the conclusions. Therefore, potential cardiovascular risk especially with long-term treatment and the clinical significance of lipid changes due to tofacitinib in RA patients are currently unknown and that is of concern.

GI perforations*:* 19 cases of GI perforations were adjudicated by 2 gastroenterologists. In total, 10 cases (including 1 death) were adjudicated as definite or probable GI perforation (incidence rate 0.177) while no cases were reported with adalimumab or placebo. The occurrence of gastro-intestinal perforation in patients treated with tofacitinib is of concern given that it is potentially life-threatening.

Hepatic disorders: hepatic enzymes increases were commonly reported. One case of death due to hepatic and lung neoplasm has been reported. More cases of hepatic disorders have been reported in Asian population. The applicant proposed a contraindication in severe hepatic impairment due to the pre-existing immunologic impairment in these patients and the extensive hepatic metabolism of tofacitinib. Of note, effects on the liver, on the gastrointestinal tract (necrosis, erosion, dilation, haemorrhage) and the lung (interstitial inflammation) were also observed in the animals during the non-clinical programme.

Risk of DILI*:* The incidence rates of >3xULN ALT elevation (including 5xULN and 10x ULN) is still greater than with adalimumab (even if the analysis is restricted to patients with normal baseline value of ALT). In addition, given the findings in one subject of biochemical abnormalities that met the criteria for Hy's law with no definitive alternative causation, the potential for tofacitinib to cause DILI cannot be ruled out. The observation that the biochemical test values worsened following discontinuation does not exclude this as representing a case of DILI. Additional data submitted from monotherapy study A1069 in methotrexate naïve patients suggested that the increased incidence of ALT elevations may be related to combination therapy of tofacitanib with methotrexate which is the proposed posology.

Haemoglobin decrease: overall in the all phase 3/LTE studies, 28 patients had potentially life threatening decreases in haemoglobin. This is a rare but worrisome event. A decrease in red blood cells and reticulocytes was also reported in animals. The responses provided by the applicant indicated that the majority of these incidences were decreases in Hb of >3g/dL and not falls of Hb to <7g/dL. In

addition, there is no consistent dose-exposure relationship.

Death: Safety data on fatal events were updated extending for the period until 19 April 2012. In total, 45 deaths occurred in tofacitinib-treated patients in phases 2, 3 and LTE studies. Three additional deaths have been reported with tofacitinib (42 deaths occurred for the period until 29 September 2011): one death with tofacitinib 5 mg BID and two with tofacitinib 10 mg BID in the LTE studies. The causes of deaths are not known. In total, the updated data confirm an increase of fatal events with tofacitinib.

Elderly: The data provided demonstrated that an increase of AE in elderly patients, particularly the percentages of SAE, with tofacitinib cannot be excluded.

Race: Overall, the safety findings suggest that Asians are more sensitive to certain tofacitinib induced side effects. There is a high incidence rates of ILD and opportunistic infections observed in Asian patients across the development programme and the literature evidence that suggests that Japanese patients may be more at risk of these AEs.

Safety profile of two doses of tofacitinib: the safety data with the high dose of 10 mg BID are of concern; in general, more undesirable effects were observed with the dose of 10 mg BID, in particular more infections, malignancies or laboratory findings. However, the exposure with this dose was clearly inferior when compared to 5 mg BID dose, especially in the long term extension studies rendering the comparison more difficult. However, the incidences of adverse events were regularly higher with this high dose. Safety data on the 5 mg BID dose are neither reassuring. Relevant number of deaths occurred with this dose, numerous cases of infections, opportunistic infections, malignancies, significant lipids increases, 4 cases of GI perforation, potential life threatening lymphopenia (6), liver enzymes, and CPK changes etc. In addition, one death due to infection has been reported in a patient treated with 3 mg BID dose.

2.6.2. Conclusions on the clinical safety

In general, patients with rheumatoid arthritis are at a higher risk of infection and cardiovascular disease and with higher mortality rate than adults in the general population. This is likely due to both altered immunological functions (as a consequence of disease) as well as other factors, including treatments for the condition.

The tofacitinib development program provided safety data from almost 5000 subjects, however with limited long-term follow up data. Tofacitinib is a first in class inhibitor of JAK1, JAK3 and to a lesser extent JAK2. JAK-3 is an integral component of the cytokine receptor for the cytokine family of IL4, IL7, IL9, IL15 and IL21. The non-clinical data demonstrated a highly selective effect of tofacitinib on T cell proliferation and differentiation. Together with a functional pharmacodynamic effect, decreases in NK cells, CD8+ and CD4+ cells were also observed in the non-clinical studies and these effects were not considered to be completely reversible.

In the Phase 3 development programme, there was an high incidence of serious infections and opportunistic infections. The spectrum of opportunistic infections included Pneumocystis Carinii, Cryptococcus and CMV and was considered to be indicative of impaired cell mediated immunity. In some cases the infections were associated with significant lymphopaenias. Further assessment of these adverse events was limited as lymphocyte subset data, in particular T-cell subset data was not systematically collected in the clinical development programme and therefore could not be adequately assessed.

In addition, the functional effects of tofacitinib on the immune system were not adequately characterised in the development programme and CHMP were therefore not reassured that the pharmacodynamic effect of tofacitinib in the target patient population had been adequately characterised. Given the mechanism of

action of tofacitinib and the pre-clinical findings, a functional impact would be expected. Finally reversibility of pharmacodynamic effect was not considered to be adequately demonstrated.

Based on these uncertainties, the risks were not considered manageable in clinical practice. The applicant has proposed a large post-authorisation efficacy and safety study. Given the mechanism of action of tofacitinib, as well as the non-clinical and clinical study findings, this approach is however not deemed sufficient to overcome the shortcomings related to lack of monitoring, assessment of immune system functionality and assessment of the reversibility of pharmacodynamic effect, in the pre-authorisation development programme.

Other concerning aspects in relation to the safety profile relate to the incidence of gastrointestinal perforation, as well as a risk of malignancy including EBV-related lymphoma. The incidence rate of malignancy was observed to be higher in the long-term extension studies, with rates increasing between the second and third year of treatment. Also the potential for tofacitinib to cause drug-induced liver injury cannot be ruled out, given the observations that one patient met the criteria for Hy's law with no obvious alternative explanation. Tofacitinib also induces a dose-dependent increase in LDL-c leading to a potentially increased cardiovascular risk.

Overall, due to the identified and potential safety concerns, the safety profiles of both doses of tofacitinib (5 mg and 10 mg) were considered unacceptable and insufficiently characterised precluding the safe use of the medicine in clinical practice.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan. The CHMP, having considered the data submitted in the application was of the opinion that the pharmacovigilance and risk minimisation activities did not address the safety concerns.

2.8. User consultation

The applicant has provided results of the user consultation with target patient groups on the package leaflet. However, due to the CHMP's conclusion on negative benefit-risk balance for tofacitinib, these results of the user consultation are not applicable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The clinical efficacy of tofacitinib in 2nd line and 3rd line treatment of rheumatoid arthritis has been investigated in five Phase 3 studies both in combination therapy and in monotherapy.

Data on the use in combination therapy for 2nd line use demonstrate efficacy for symptoms of arthritis (ACR20), clinical remission (DAS-28) and physical function (HAQ-DI). The comparative results against adalimumab suggest similar efficacy for these parameters. Given that the majority of studies enrolled significant numbers of patients who had failed tDMARDS other than MTX, with regards to a 2nd line indication, the results are considered generally applicable to this patient population.

Regarding combination therapy with MTX in TNFi failed population (as defined by the investigator) the data showed some activity (symptoms of arthritis (ACR-20), clinical remission (DAS-28) and physical function (HAQ-DI) as, as compared to placebo. The monotherapy use in MTX intolerant patients showed statistically significant differences from placebo for symptoms of arthritis (ACR-20) and physical function (HAQ-DI), however failed to show significance for clinical remission (DAS-28).

Uncertainty in the knowledge about the beneficial effects

There is a lack of robust results for slowing of structural progression (mTSS score). Available data for the 10 mg dose showed a statistically significant effect whereas the 5 mg dose failed to show statistical significance for mTSS. For patients who advanced from placebo to active, there appeared to be some slowing of progression, however given the trial design it is difficult to quantify the magnitude of the effect. Therefore, efficacy is not considered to be robustly demonstrated for 5 mg with regards to slowing of structural progression. Data from the MTX naïve-population is not considered adequate to overcome this uncertainty given the difference in patient population.

The available data for use in monotherapy are of limited relevance for a 3rd line indication as only 16.2% of patients had prior TNFi therapy exposure. For the 2nd line indication, the monotherapy study did lack comparison to an active comparator. Although significant differences from placebo were observed for symptoms of arthritis (ACR20) and physical function (HAQ-DI), the study failed with regards to achieving DAS28<2.6 for both the 5 and 10 mg doses.

Specifically for the 5 mg BID dosing in patients with inadequate response to at least one biologic disease modifying antirheumatic drug (DMARD), which was proposed by the applicant during the assessment, the benefits on disease activity remain uncertain. Tofacitinib 5 mg BID failed to reach statistical significance for DAS28 when used in monotherapy, and results were borderline for DAS28 in the 3rd line population. The re-analyses did not provide the required reassurance that efficacy has been robustly demonstrated for DAS28 in the 3rd line setting for the 5 mg dose. Results on DAS28 in the 2nd line study 1044 should be interpreted with caution as the endpoint hierarchy had already failed and so was formally failed for DAS28 as well. Therefore overall the evidence for a benefit of the 5 mg dose on DAS28, particularly for 3rd line patients is weak.

Risks

Unfavourable effects

Patients treated with tofacitinib are at an increased risk of infections. These include serious infections, opportunistic infections, tuberculosis, herpes zoster, and severe pneumonia including cases of P jiroveci pneumonia, which are of particularly concern. Tofacitinib treatment was associated with an increased incidence of neutropenia and lymphopenia and episodes of life-threatening lymphopaenia were associated with a high incidence of serious and treated infections. Decreases in the CD4/CD8 and CD56 counts are observed with tofacitinib.

With regard to malignancies, an increased risk is observed in patients with RA treated with tofacitinib in particular with rates increased between 2nd and 3rd year of treatment.

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Significant dose-dependent increases in lipids levels have been observed, which are of concern with regards to the potential cardiovascular risk, especially with long-term treatment of tofacitinib. More cases of congestive heart failure have been reported with tofacitinib as well as hypertension.

Gastrointestinal perforations are an important identified risk. In the clinical development programme, 10 cases (including 1 death) were adjudicated as definite or probable GI perforation.

Hepatic enzymes increased were commonly reported with a high incidence rates of >3xULN ALT elevations. These increases persist even if the analysis is restricted to those with a normal baseline value. Furthermore there is a single case of potential drug-induced liver injury that meets the criteria for Hy's law and has no clear alternative explanation.

Uncertainty in the knowledge about the unfavourable effects

There is a high degree of uncertainty related to the high risk of infections as patients treated with tofacitinib developed serious and fatal opportunistic infections and the spectrum of these disorders is indicative of impaired cell-mediated immune function. This could have been anticipated considering the mechanism of action of tofacitinib with specific effects on T-cell proliferation and maturation. There is evidence that tofacitinib use is associated with an increased incidence of life-threatening episodes of lymphopaenia and that a high percentage of these episodes were associated with serious or treated infections. This incidence is particularly high in the long-term extension studies with 80% of the episodes associated with treated infection and 40% with serious infection. The spectrum of observed infections associated with the lymphopaenias could have been predicted from the mechanism of action of tofacitinib and the consequential severe impairment of cell-mediated immunity. The applicant has not presented adequate evidence of reversibility of this pharmacodynamic effect on the immune system.

Additional data submitted by the applicant, confirmed that tofacitinib has a pervasive effect on the immune system and in particular on T-cell sub-set cell counts (CD4/CD8/CD56). Significant decreases in NK cells are apparent at 6 weeks and CD8/CD4 decreases apparent after 6 months. Despite the non-clinical studies indicating similar findings, the applicant did not collect WBC sub-set data in the P3 studies. This therefore limits any proposed risk minimisation strategies to attempt to manage the increased infection risk. The applicant's proposed strategy to attempt to reduce the risk of opportunistic infections by using a cut-off for total lymphocyte cell counts of 500 cells/mm^3 is not endorsed.

Furthermore the functional impact of tofacitinib on the immune system has not been adequately characterized. A high incidence of TB occurred despite the incorporation of TB screening and use of isoniazid in the development program. The presence of extra-pulmonary dissemination is again suggestive of impaired cell-mediated immunity. There is also a clear concentration-related increased incidence of serious and treated infections. This was not visible for opportunistic infections.

The incidence of malignancies with tofacitinib use was higher in long-term extension studies, in particular with rates increased between 2^{nd} and 3^{rd} year of treatment. The applicant considered different mechanisms (direct effect on JAK inhibition or indirect mechanisms of decreased immune surveillance and background RA disease) of occurrence of carcinomas, but no mechanism has been determined for the time being. The extent of risk related to the long-term use is not known.

There is major concern with regards to the observations of a potential case of drug-induced liver injury. This occurred in a 32 year old female whose liver function abnormalities met the criteria for Hy's law. Whilst the hepatic injury worsened for an additional 2-3 months after discontinuing the drug, the initial elevations occurred whilst on tofacitinib. This together with the observation that the incidence of >x3 ULN ALT elevations are higher in patients treated with tofacitinib as compared to placebo and adalimumab (even if the analysis is restricted to patients with a normal baseline) raises major concerns with regards to the likelihood of tofacitinib causes DILI.

RA patients are already at increased risk of cardiovascular diseases. According to the literature, vascular risk is increased early in the course of RA, perhaps reflecting subclinical inflammation in the pre-articular phase. Lipid biochemical features are intimately and reciprocally, linked to inflammation to ensure metabolically efficient host defence. In consequence, active RA is associated with reduced serum levels of total, HDL and LDL cholesterol, which may then be paradoxically elevated by effective therapy. With tofacitinib treatment, it is unknown how the additional, significant increases in lipids levels seen in the clinical trials with both doses would exacerbate the CV status of patients. CV adverse events like congestive heart failure and hypertension have been reported in treated patients. Particularly, concerns are raised with long-term treatment of tofacitinib. The applicant provided an analysis of lipid parameters changes and a potential cardiovascular risk. A relationship between lipid parameter changes under tofacitinib treatment and CV risk consequences, remains currently not known, in particular for long-term treatments.

Blood CK levels increase has been observed with tofacitinib. In addition, the data on reported cases are not reassuring with regards to the risk of rhabdomyolysis. Cases of rhabdomyolysis occurred in patients treated with tofacitinib while no cases have been observed with placebo and adalimumab. For both cases, a causal relationship between the reported events and Tofacitinib cannot be excluded. The CK mean significantly increased at Month 12 in Tofacitinib groups, with or without statins.

Benefit-risk balance

Importance of favourable and unfavourable effects

The efficacy has been only demonstrated in symptomatic treatment of rheumatoid arthritis as prevention of structural damage has not been robustly shown. This lack of structural effect might be explained by tofacitinib pharmacodynamic properties. Structural damage in rheumatoid arthritis is related both to cartilage damage and bone erosion.

Consequently, the benefits of tofacitinib appear inferior to those observed with available therapies that are licensed for treatment of rheumatoid arthritis and recommended according to treatment guidelines. As these available therapies have shown both clinical efficacy and inhibition of structural damage, the benefit of a new treatment that would act only on signs and symptoms is questionable.

Tofacitinib is a potent immunosuppressive drug which acts as an inhibitor of JAK1, JAK3 and, to a lesser extent, JAK2 causing pervasive immunosuppression but specifically affecting T-cell development and maturation. Patients treated with tofacitinib developed serious potentially fatal opportunistic infections. The spectrum of these disorders is clearly indicative of impaired cell-mediated immune function. This could have been anticipated considering the mechanism of action. The limited data collected in the clinical development programme indicated a significant decrease in CD3 cells occurring at 6 months with treatment and continuing with long-term treatment. CD56 cell decreases also occurred. There is inadequate demonstration of reversibility of the pharmacodynamic effect. Furthermore, the functional impact of tofacitinib on the immune system has not been adequately characterised.

With regards to serious and opportunistic infections, the white blood cell subtypes responsible for the increased incidence of infection have not been adequately characterised. Analyses are limited as T-cell subset data was not collected in the P3 studies. This lack of data greatly limits the conclusions that can be made and any risk management strategies to try and reduce the rates of serious/fatal opportunistic infections.

There is a high likelihood that tofacitinib will cause DILI. Within the restricted clinical trial population there is already a case of potential DILI for which there was no alternative satisfactory explanation. In addition the higher incidence of ALT elevations of >x3 ULN is considered to be a sensitive indicator of the potential for a drug to cause DILI.

Numerous other major safety concerns precluding the marketing authorization of tofacitinib have been identified (deaths, malignancies, lymphomas, lipids and cardiovascular risks, gastrointestinal perforations). Long term safety data are lacking and this is also considered as a major drawback since RA patients are intended to be treated at long term.

The range of serious side-effects experienced with use of tofacitinib in the clinical development programme are considerably more serious and worse than that generally reported for the TNF inhibitors. In particular the increased incidence of serious/opportunistic infections associated in some cases with mortality or lack of resolution and the morbidity associated with gastrointestinal perforations and malignancies are of major concern.

The applicant during the procedure restricted the proposed dosing to 5 mg BID in order to address safety concerns and trends seen with higher dosing. However, the 5 mg BID dosing appears inferior to higher doses in terms of efficacy. In particular the lack of evidence with regards to the prevention of structural damage with this dosing in the target population is of concern. Therefore, the restriction in dosing, whilst intended to address safety, negatively impacts the efficacy conclusion.

Benefit-risk balance

The benefit of tofacitinib in the dose of 5 mg bid in the proposed patient population (i.e. patients who have had an inadequate response to at least one biological DMARD) is rather small since it has only demonstrated an effect on signs and symptoms of rheumatoid arthritis. The evidence for an effect of tofacitinib on prevention of structural damage progression in the proposed patient population using the dose of 5 mg bid is insufficient. The magnitude of effect in this population cannot be sufficiently quantified considering the limited data available in the proposed patient population and concerns over the possibility to extrapolate from the available data from other patient populations in the clinical trial program. In addition, there is concern that the statistical methods employed to handle patients who discontinue from randomised treatment may overestimate the effects.

The functional impairment caused by tofacitinib on the immune system has not been adequately characterised. 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. In addition to the increased risk of infections, there are a number of other safety major objections in particular GI perforations, malignancies and drug-induced liver injury that remain unresolved. Consequently, there are uncertainties surrounding the magnitude of the risks and their management in clinical practice, which are not offset by the benefits of treatment.

Therefore, the numerous significant safety issues outweigh the small benefit. The overall benefit risk balance of tofacitinib 5 mg BID for patients with inadequate response to at least onebiologic disease modifying antirheumatic drug (DMARD) is therefore negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Xeljanz (with or without

methotrexate) in the treatment of "moderate to severe active rheumatoid arthritis (RA) in adult patients who have had an inadequate response or are intolerant to previous therapy with at least one biological DMARD. Tofacitinib can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tofacitinib has been shown to inhibit the progression of joint damage as measured by X-ray and to improve physical function", the CHMP considers by consensus that the safety and efficacy of the above mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The evidence for an effect of tofacitinib on prevention of structural damage progression in the proposed patient population (i.e. patients who have had an inadequate response or are intolerant to previous therapy with at least two other DMARDs including at least one biological DMARD) using the dose of 5mg bid is insufficient. The magnitude of effect in this population cannot be sufficiently quantified considering the limited data available in the proposed patient population and concerns over the possibility to extrapolate from the available data from other patient populations in the clinical trial programme. In addition, there is concern that the statistical methods employed to handle patients who discontinue from randomised treatment may overestimate the effects.
- 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.
- 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 programme is fully applicable. Consequently, there are uncertainties surrounding the magnitude of the risks and their management in clinical practice, which are not offset by the benefits of treatment.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Re-examination of the CHMP opinion of 25 April 2013

Following the CHMP conclusion that Xeljanz was not approvable for the following indication:

Tofacitinib, in combination with methotrexate (MTX), is indicated in for treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have had an inadequate response or are intolerant to previous therapy with at least two other disease-modifying antirheumatic drugs (DMARDs) including at least one biological DMARD MTX. Tofacitinib can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tofacitinib has been shown to inhibit the progression of joint damage as measured by X-ray and to improve physical function,

the applicant submitted detailed grounds for the re-examination of the grounds for refusal on 13 June 2013.

Detailed grounds for re-examination submitted by the applicant

Following a request from the applicant at the time of the re-examination, the CHMP convened an Ad Hoc Expert Group inviting the experts, including patient representatives, to provide their views on the questions posed by the CHMP, taking into account the applicant's response to the grounds for refusal. The CHMP requested the advice of the Pharmacovigilance Risk Assessment Committee (PRAC) on specific questions related to the proposed RMP proposals. The PRAC's recommendation on specific CHMP questions was issued on 11 July 2013.

The applicant presented their detailed grounds for re-examination in writing on 13 June 2013 and at an oral explanation on 22 July 2013.

Summary of applicant's detailed grounds for re-examination

The Applicant requested a re-examination of the CHMP's opinion on Xeljanz , to re-assess the benefit/risk in the treatment (in combination with methotrexate (MTX)), of moderate to severe active rheumatoid arthritis in adult patients who have had an inadequate response or are intolerant to previous therapy with at least one biological DMARD. Tofacitinib can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tofacitinib has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.

The following issues were addressed by the Applicant:

- Clinically meaningful efficacy has been demonstrated across a variety of endpoints and lines of therapy ranging from MTX - naïve to bDMARD IR patients.
- Efficacy in prevention of structural damage progression has been established in MTXnaïve (primary endpoint) and in MTX-IR (secondary endpoints and sensitivity analyses) populations.
- The magnitude of effect in the 3rd line population is consistent with that observed with rituximab in a 3rd line population.
- The safety profile of tofacitinib in the 3rd line population is consistent with the overall population.
- The safety profile of tofacitinib 5 mg BID is well defined for a drug at pre-authorization stage. This profile is familiar to HCPs experienced in treating patients with immunomodulatory and anti-inflammatory DMARDs and can be managed according to the proposed SmPC and RMP.

The applicant was of the opinion that tofacitinib 5 mg BID will therefore provide an additional therapeutic option with a unique mechanism of action, oral route of administration, proven efficacy and acceptable safety profile for patients with moderate to severe active RA who have had inadequate response to or are intolerant to previous therapy with at least one bDMARD. These treatment-refractory patients require new treatment options with novel mechanisms of action.

The indication proposed by the applicant in the re-examination application was as follows:

"*Tofacitinib, in combination with methotrexate (MTX), is indicated for treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an inadequate response or are intolerant to previous therapy with at least one biological DMARD. Tofacitinib can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tofacitinib has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function*".

The Applicant addresses specifically the CHMP's initial grounds for refusal:

Ground 1

The evidence for an effect of tofacitinib on prevention of structural damage progression in the proposed patient population (i.e. patients who have had an inadequate response or are intolerant to previous therapy with at least one biological DMARD) using the dose of 5mg bid is insufficient. The magnitude of effect in this population cannot be sufficiently quantified considering the limited data available in the proposed patient population and concerns over the possibility to extrapolate from the available data from other patient populations in the clinical trial programme. In addition, there is concern that the statistical methods employed to handle patients who discontinue from randomised treatment may overestimate the effects.

Applicant's position

Review of the primary endpoints of the two tofacitinib studies of radiographic progression of structural damage confirms the efficacy of tofacitinib 10 mg BID in patients with an inadequate response to methotrexate, and of both doses of tofacitinib in the methotrexate-naïve population. Pre-specified secondary analyses of the MTX IR data (Study A3921044) support the structure benefits of tofacitinib 5 mg in this treatment population. In addition, a sub-population of patients enrolled in Study A3921044 was also bDMARD IR, and their data shows reduction of progression by tofacitinib 5 mg relative to placebo. Thus, tofacitinib consistently demonstrates inhibition of structural damage progression across various RA treatment populations including MTX naïve, MTX IR, and bDMARD IR patients (3rd line). Tofacitinib's structure effect in the MTX IR population is similar to a TNF inhibitor and an interleukin-6 (IL-6) receptor inhibitor, and it's effect in the MTX naïve and bDMARD IR populations is similar to that seen with rituximab, an approved B cell lytic agent used to treat RA patients who have had an inadequate response to one or more TNF inhibitor therapies (3rd line). In addition, there is a strong biologic and mechanistic rationale supporting tofacitinib's effectiveness in patients at different stages of RA disease.

Biologic Rationale and Mechanistic Explanation for Tofacitinib's Effectiveness across RA Lines of Therapy

Tofacitinib's effectiveness across lines of treatment is supported by evidence that the synovial changes observed in early disease are representative of chronic disease. That is, within a given patient, evidence from sequential biopsies has demonstrated similarity of synovial histopathology between joints, and stability over time (Weyand et al, 2003). As Tak concludes, the finding that the features of the synovium are similar in early RA and longstanding disease indicates that no arguments currently exist for the effect of therapeutic intervention on synovial inflammation varying between different stages of the disease (Tak, 2001).

Drug therapy that changes the immunopathological behaviour of the rheumatoid synovium is critical to the control of inflammation and damage. Common important mediators of osteoclastic bone destruction are the receptor activator of nuclear factor kappa B (RANK), and its associated ligand, RANKL. However, inhibition of structural damage has been shown with a variety of DMARDs with a range of mechanisms of action.

For example:

Abatacept, a biologic DMARD which inhibits interaction of T cell costimulatory cell surface molecules, is effective in treatment of TNF IR (Genovese et al, 2005). However, in this patient population abatacept treatment did not impact the cellular constituents of the synovium, but rather significantly reduced interferon (IFN) gamma gene expression and showed a trend towards reduction in expression of multiple inflammatory cytokines including IL-6 and TNF alpha. Matrix metalloproteinases (MMP) and

RANK/RANKL were decreased, consistent with an inhibitory effect on cartilage and bone destruction (Buch et al, 2009).

In contrast, TNF inhibitors have been shown to reduce synovial macrophages, without an effect on the T cell population, and nonetheless have similar inhibition of RANK signaling and bone and cartilage damage (Catrina et al, 2005).

Administration of rituximab, a cytolytic antibody targeted to the cluster of differentiation (CD)-20 antigen on B lymphocytes, is associated with a reduction in synovial B cells, but no change in macrophages or CD3+ cells, or in expression of inflammatory cytokines TNF alpha and IL-6 (Kavanaugh et al, 2008). However, reductions in synovial expression of RANKL and numbers of osteoclast precursor cells have been observed (Boumans et al, 2012).

Tofacitinib, in the rat antigen induced arthritis model, decreased T cell infiltrate and RANKL in the affected paws (LaBranche, 2012), in association with inhibition of bone erosion.

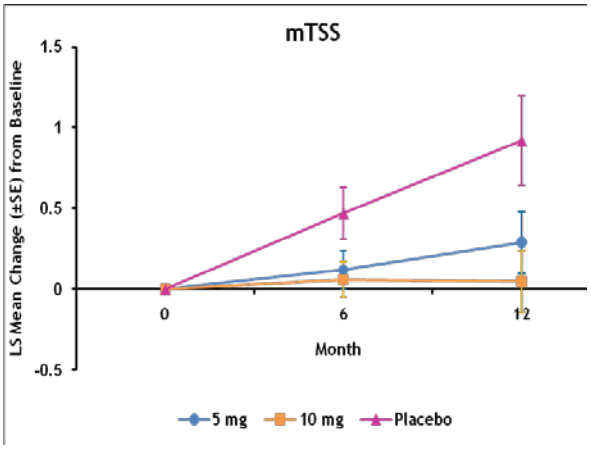
Tofacitinib inhibits RANKL production in activated human T cells (LaBranche 2012). In addition, tofacitinib inhibits human RA synovial expression of chemokine CXCL10 mRNA and corresponding plasma concentrations of the interferon-inducible protein-10 (IP-10) (Study A3921073), which induces RANKL production by human activated T cells and fibroblast-like synoviocytes (Lee, 2013). In MTX IR patients, tofacitinib reduced synovial expression of MMP-3 mRNA and also showed a trend towards reduction in urine carboxyterminal telopeptide of type II collagen (uCTXII), which are biomarkers associated with cartilage damage (Study A3921073). Therefore, tofacitinib's effects on biologic mechanisms explain its property of promoting the preservation of bone and cartilage.

Tofacitinib Inhibits Progression of Structural Joint Damage

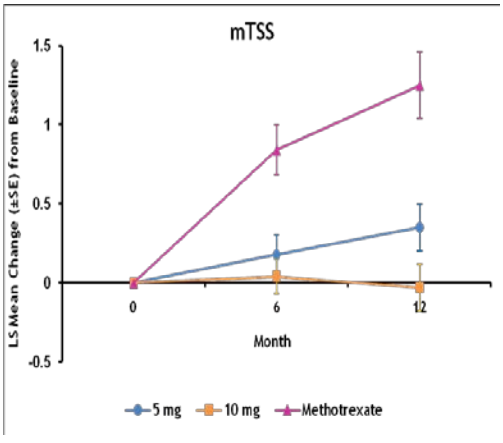
Evidence of tofacitinib's inhibition of structural damage progression has been provided in patients who have had an inadequate response to MTX (Study A3921044) and who are MTX naïve (Study A3921069). Both tofacitinib studies demonstrated reduction in mTSS (primary endpoint) and radiographic joint space narrowing (JSN, a component of the mTSS), which is evidence of cartilage preservation (Figure 1). In Study A3921044, JSN was significantly different from placebo ($p<0.05$) at Month 12 for both tofacitinib doses; in Study A3921069, JSN was significantly different from MTX for both tofacitinib doses at Months 6 and 12.

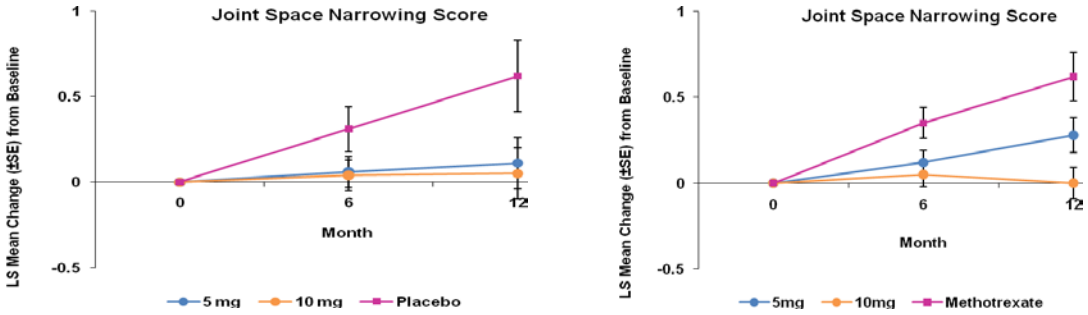
Figure 1. Modified Total Sharp Scores and Joint Space Narrowing Scores (Change from Baseline) at Month 6 and 12– Studies A3921044 and A3921069

A3921044



A3921069

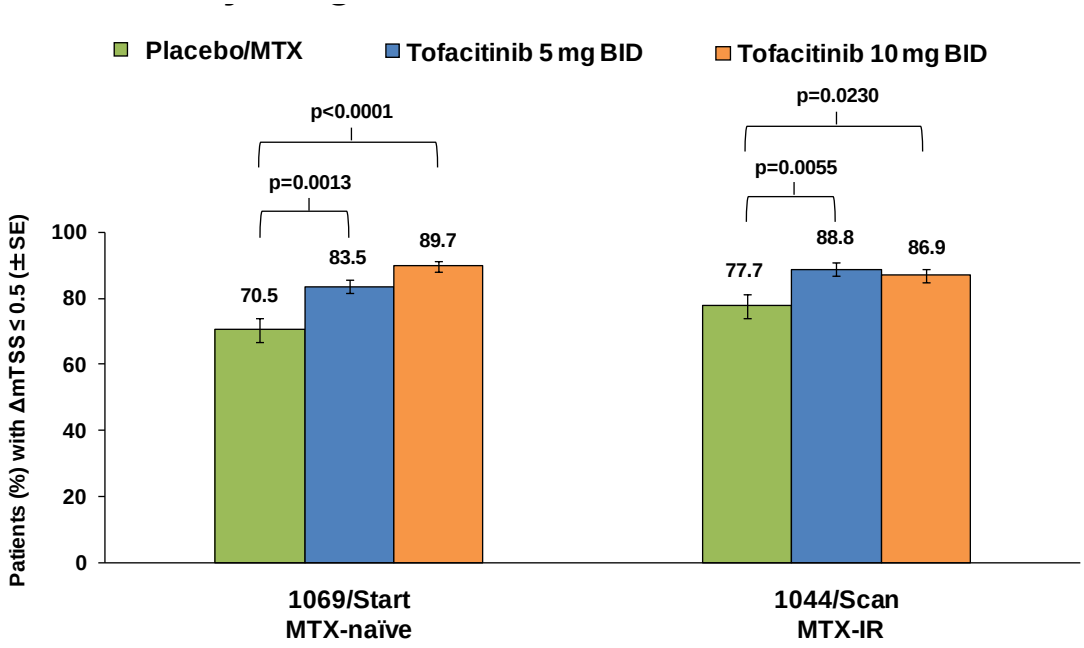




LS = least square, SE = standard error, mTSS = modified total sharp score

While the primary endpoint narrowly missed achieving statistical significance for the 5 mg dose in the MTX IR Study A3921044, the pre-specified secondary analysis of the proportion of patients not showing radiographic progression, defined a priori as change from baseline ≤0.5 units, demonstrated statistical significance for both tofacitinib doses in comparison to the control group in both studies (Figure 2). In Study A3921044, a non-parametric rank analysis was performed as a pre-specified sensitivity analysis, and showed significant difference from placebo for tofacitinib 5 mg. These secondary analyses, which are not sensitive to extreme values or imputation methodology, indicate that tofacitinib 5 mg inhibits progression of structural damage.

Figure 2. Proportion (%) of Tofacitinib-Treated Patients with No X-Ray Progression at Month 6

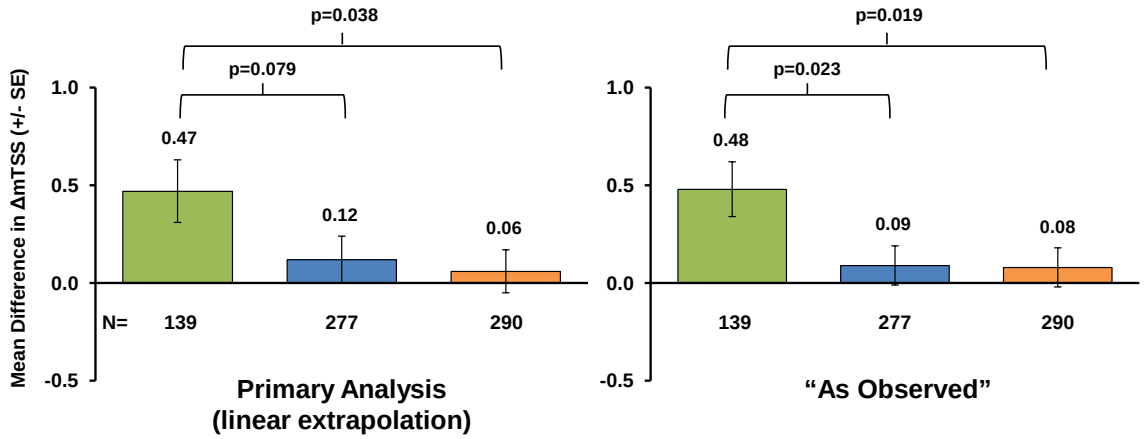


mTSS = modified total sharp score, MTX = methotrexate, IR = inadequate responder. SE = standard error

Regarding the concern about bias in estimation due to extrapolation of data from drop-outs or patients who advanced, note that a total of 20 (approximately 9% of those extrapolated) patients had their Month 6 data extrapolated from Month 3 due to discontinuation. Therefore the majority of extrapolation was done because patients met the criteria for advancement at Month 3. This advancement strategy was mandated by an ethical requirement to limit exposure to placebo. Linear extrapolation, an analytical technique that is used extensively in RA trials, is an effective way to equate rate of progression in these patients to those who were measured at Month 6, as linear extrapolation takes the rate of change over time and multiplies it by time to give the effect at a given time (Month 6). This assumes that the 3 month change is representative of the 6 month change that would have been observed in these patients in the absence of advancement, which is a reasonable assumption, given the short duration of time involved, and which is supported by secondary and sensitivity analyses.

These secondary or sensitivity analyses that assessed the impact of extrapolation and missing data all indicate that neither the extrapolation nor the missing data altered the interpretation of the results. Notably, the similarity of the extrapolated and observed results (Figure 3) in the tofacitinib arms supports that extrapolation is justified in Study A3921044. Additionally, the extrapolation method would not have significant influence on the results from the analysis of proportion of patients with no progression and the results from this analysis (Figure 2) show a similar pattern of effect compared with the analysis of mean change in mTSS, the primary endpoint.

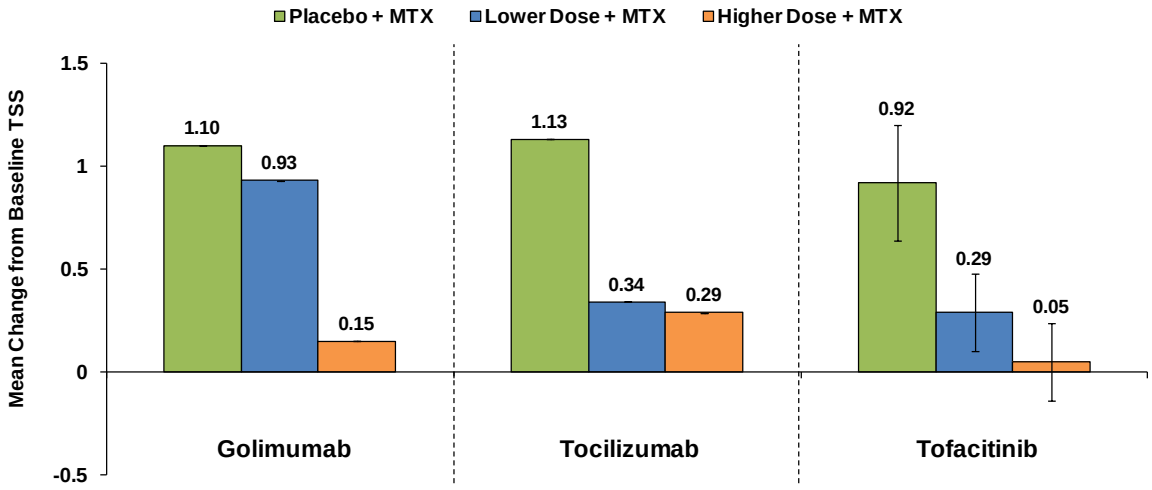
Figure 3. Effect of Extrapolation on Tofacitinib Structure Analysis, Mean Change in mTSS at Month 6 – Study A3921044



mTSS = modified total sharp score, MTX = methotrexate,. SE = standard error, N = number of patients

The applicant previously shown that tofacitinib's structure modifying effects appear similar in magnitude to those reported from studies of a TNF inhibitor, and an IL-6 receptor inhibitor, in a MTX IR population (Figure 4).

Figure 4. Recent Biologic DMARD Structure Studies: Comparison to Tofacitinib MTX-IR Month 12 Data from Study A3921044



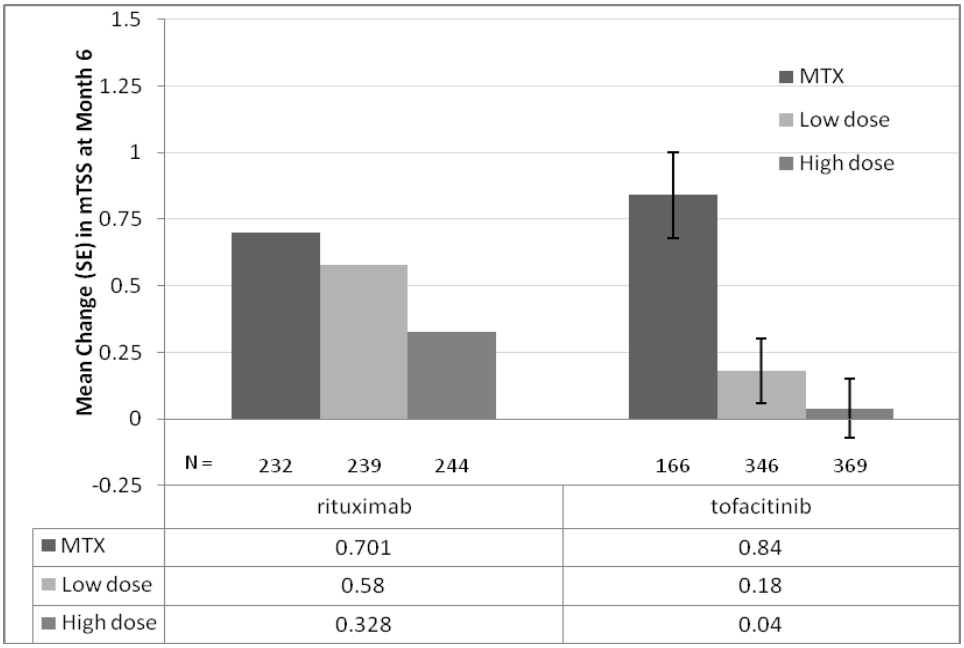
Tocilizumab used Genant-modified Total Sharp Score; Tocilizumab: Kremer et al, 2011; Golimumab: Emery et al, 2011; TSS = total sharp score; MTX = methotrexate, IR = inadequate responder

To illustrate tofacitinib's structure modification potential in the proposed 3rd line treatment population, the company showed the A3921044 bDMARD IR subpopulation data side-by-side with that of rituximab, an approved bDMARD that has shown inhibition of structural damage progression in patients with an inadequate response to a TNF inhibitor (Cohen et al, 2006 and Keystone et al, 2009). For further reference, the applicant showed the MTX naïve structure data for tofacitinib (Study A3921069) and rituximab (Tak, 2011).

Use in Methotrexate Naïve RA Patients: Comparing Tofacitinib and Rituximab

Rituximab has structure modification studies in both MTX-naïve (IMAGE, Tak, 2011) and TNF-IR (REFLEX, Cohen et al, 2006) populations, and thus provides a point of reference for tofacitinib in each of these populations. In the MTX naïve studies (A3921069 and IMAGE), the magnitude of progression of structural damage is similar in the methotrexate control groups, but proportional reduction in structural damage appears to be greater with tofacitinib than for rituximab (Figure 5). At approximately 6 months, the higher, but not the lower, rituximab dose group was significantly different from methotrexate control ($p<0.05$). In Study A3921069, both the 5 mg ($p=0.0006$) and 10 mg ($p<0.0001$) tofacitinib doses were superior to methotrexate. These comparisons remained significant at 12 months.

Figure 5. Change from Baseline in Modified Total Sharp Scores at Month 6, Rituximab and Tofacitinib, Studies in Methotrexate Naïve Patients



	rituximab	tofacitinib
MTX	0.701	0.84
Low dose	0.58	0.18
High dose	0.328	0.04

Source: Tofacitinib data from Study A3921069; IMAGE Rituximab data (Tak, 2011); mTSS = modified total sharp score, MTX = methotrexate, SE = standard error

Both studies recruited similar populations with predominantly early RA disease (majority with <2 years RA duration and no prior DMARD experience) and high disease activity, but low mean baseline radiographic damage scores (mTSS).

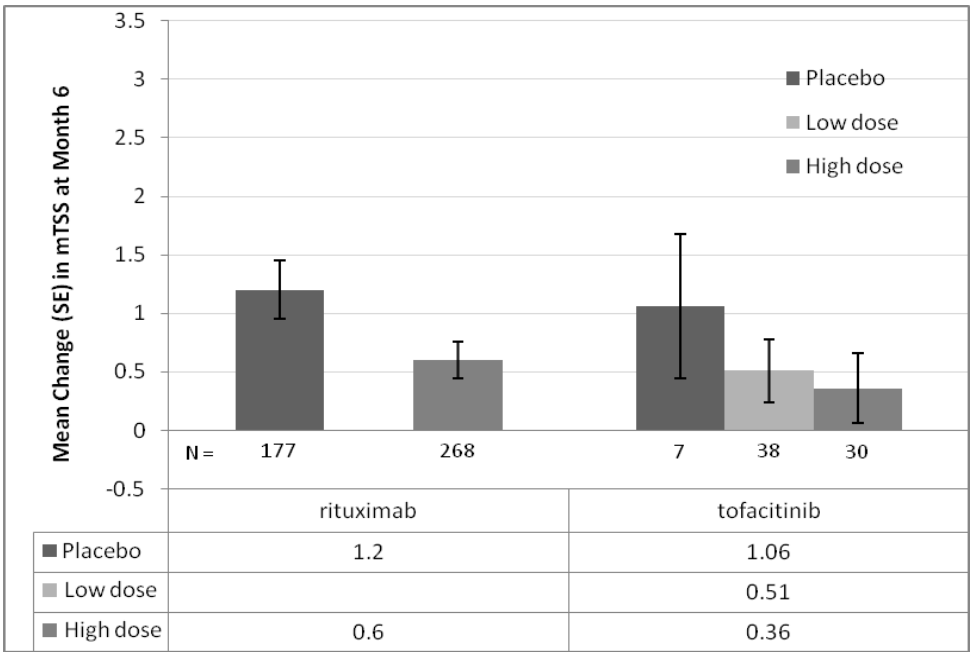
In the IMAGE study, patients were randomised to titrated MTX alone (control group) or MTX in combination with rituximab administered as a lower (500 mg x 2 infusions courses) or a higher (1000 mg x 2 infusions courses) dose. In Study A3921069, patients were randomised to either tofacitinib administered as DMARD monotherapy, 5 or 10 mg twice daily, or to MTX alone (control group). Control and experimental agent-treated patients in IMAGE and Study A3921069 continued their assigned treatment for the first 12 months of study participation. Missing structure data were imputed by linear extrapolation.

Use in bDMARD Inadequate Responder RA Patients (3rd Line): Comparing Tofacitinib and Rituximab

Additionally, the applicant compared the effectiveness of tofacitinib with rituximab in inhibiting

structural damage in a 3rd line treatment population. In this comparison, the inhibition of structural damage progression is similar between tofacitinib and rituximab, with apparent, but not statistically significant, reduction relative to placebo (~50%) associated with tofacitinib 5 mg (Study A3921044) and rituximab (REFLEX, Cohen et al, 2006) at approximately 6 months (Figure 6).

Figure 6. Change from Baseline in Modified Total Sharp Score at Month 6, Rituximab and Tofacitinib in Biologic DMARD Inadequate Responding Patients



	rituximab	tofacitinib
Placebo	1.2	1.06
Low dose		0.51
High dose	0.6	0.36

Source: Tofacitinib data from Study A3921044; REFLEX Rituximab 24 week data (Cohen et al, 2006); mTSS = modified total sharp score, SE = standard error

Patients enrolled in the rituximab REFLEX study were typical of TNF inhibitor inadequate responders by having longstanding RA disease (mean ~12 years) and by the number of TNF inhibitor agents previously taken (mean ~1.5) (Cohen et al, 2006). Approximately 60% and 30% of patients had an inadequate response to one or two TNF inhibitors, respectively. Patients had high disease activity and disability scores. Within Study A3921044, seventy-five patients had experienced a prior inadequate response to a bDMARD and had radiographic data. Baseline characteristics of these Study A3921044 bDMARD IR patients were similar to those of patients enrolled in the REFLEX trial.

In REFLEX, rituximab was administered as 2 infusions of 1000 mg (1 course of therapy) in comparison to placebo, both on a background of MTX. Rescue therapy for non-responders was allowed as early as 16 weeks, and 80 of 209 placebo patients (38%) received rescue with rituximab, and 16 withdrew, by the 6 month time point. Of patients assigned to the rituximab treatment group, 53 withdrew early and only one required rescue (usual care). In Study A3921044, approximately half of placebo patients were nonresponders and were rescued with tofacitinib 5 or 10 mg twice daily at 3 months; a smaller proportion of tofacitinib treated patients were nonresponders at 3 months.

Structure data from REFLEX was reported as-observed at Week 24. The primary structure analysis in Study A3921044 used linear extrapolation from 3 months to 6 months for placebo nonresponders. For the tofacitinib treated non-responding patients, radiographic scores were also extrapolated from 3 months to 6 months for the primary analysis; however, these patients remained on their assigned treatment and continued to have radiographs performed out to 12 months. Therefore, the applicant is able to show the as-observed tofacitinib data (Figure 6), corresponding to the REFLEX data. Mean

changes in mTSS appear to be similar for the rituximab and tofacitinib treatment groups (Figure 6).

Applicant's conclusions

Examination of primary and secondary endpoints in Studies A3921044 and A3921069 demonstrates that tofacitinib inhibits progression of structural damage in two distinct RA treatment populations. The consistency of this evidence across both populations is expected in view of earlier findings that synovial immunohistopathology is similar in early and late stages of the disease (Tak, 2001). Analysis of the subset of patients from Study A3921044 who were bDMARD IR reveals a magnitude of effect similar to that observed with rituximab in TNF IR. These patients, with treatment-refractory disease, had substantial accumulated damage, and showed a greater progression of damage than the MTX IR population, as measured by mTSS. Data support that tofacitinib ameliorates damage progression even in this 3rd line treatment population.

An expert statement has been prepared by rheumatologists in clinical practice in the EU, informed by data from the clinical development of tofacitinib. In this expert statement, the rheumatologists provide their opinion on the inhibition of radiographic progression.

Ground 2

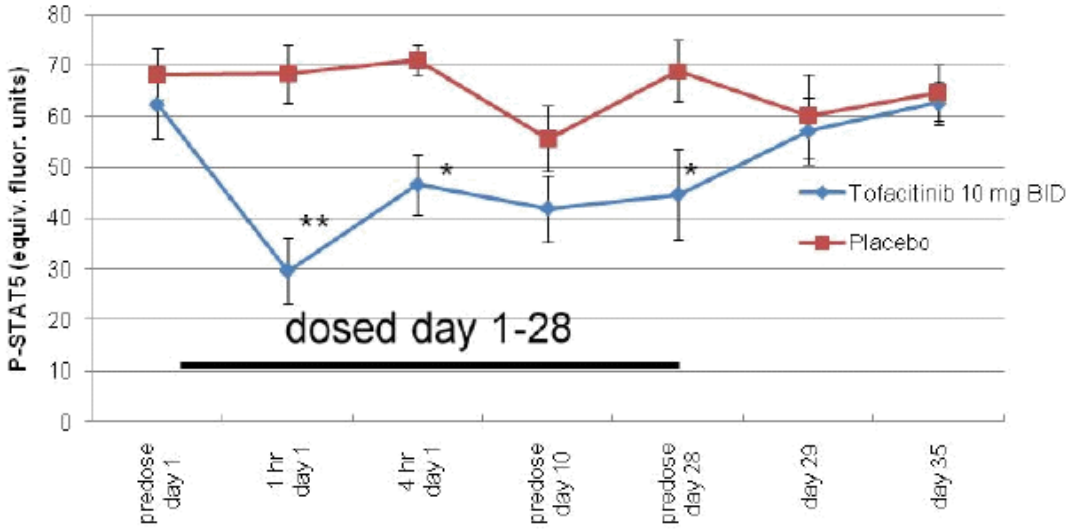
There are significant and unresolved concerns regarding the number of serious and opportunistic infections observed with tofacitinib in the clinical studies, which are indicative of impaired cell-mediated immunity. These risks are related to the primary pharmacology of this first in class agent. The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

Applicant's position

Pharmacodynamic data of lymphocytes

The Applicant provided data from in-vitro PK-PD models and ex-vivo studies, indicating that the PD effect of tofacitinib on cellular immunity (CD8) and JAK dependent cytokine signalling is partial and reversible shortly after treatment withdrawal (i.e. within 2 weeks) (see Figure 7 & 8 below).

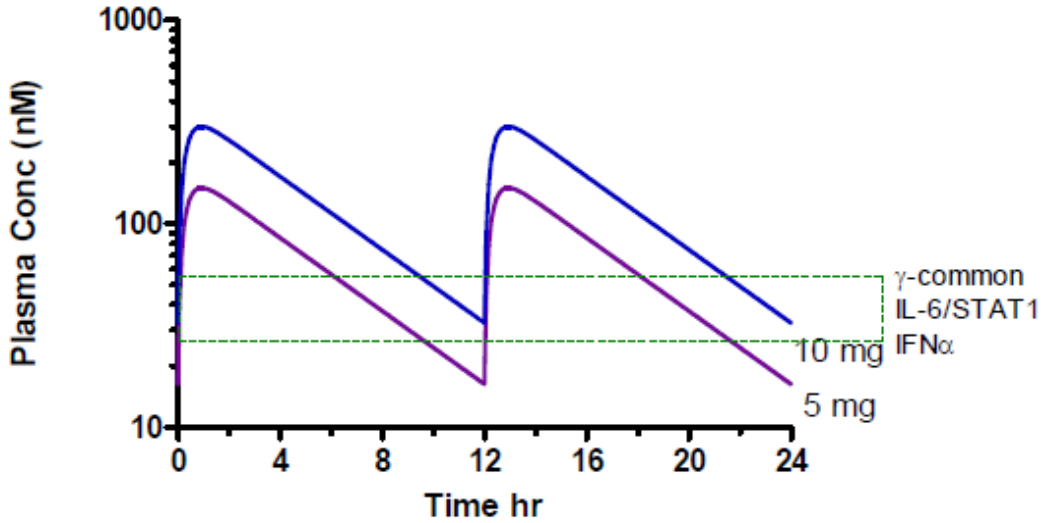
Figure 7 **Time Course of Mean p-STAT5 Levels in CD8 T Cells from Tofacitinib or Placebo Treated RA Patients with ex vivo IL-15 Challenge (A3921073)**



* P < 0.05, **p < 0.005 change from day 1 pre-dose relative to placebo. Mixed effect model with treatment, visit, and treatment by visit interaction as factors and baseline (day 1) as a covariate, subject as a random effect.

Error bars are standard error of the mean
BID = twice daily, p-STAT = signal transducer and activator of transcription, CD = cluster of differentiation, RA = rheumatoid arthritis

Figure 8 **Tofacitinib Partially and Reversibly Inhibits Multiple JAK Dependent Cytokine Signaling Pathways**



IL=interleukin; STAT=signal transducer and activator of transcription; IFNα=interferon α

It was postulated that immune-modulating effect of TNF-I and tocilizumab are anticipated to be more prolonged, considered that these drugs are often monoclonal antibodies with a prolonged half-life of several weeks, compared to the short half-life of small protein tofacitinib of 3 hrs.

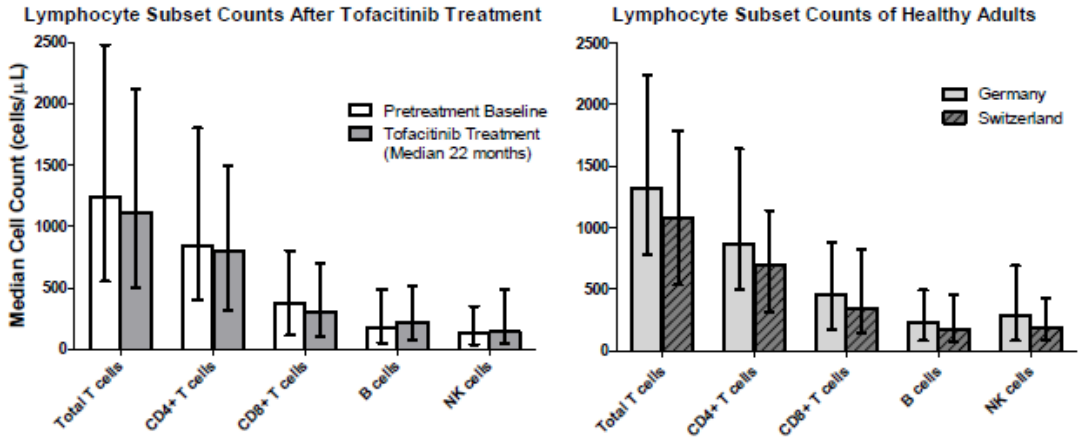
Furthermore, the Applicant provided cellular immunity data from subgroups of subjects treated with tofacitinib in Phase II setting. In rodents and monkeys, there was a significant drop from baseline in CD3/4/8 levels compared to baseline of about 30% at high doses, whereas this was overall more modest in RA patients at a low 5 mg dose. In all species, NK cells dropped significantly (-20-40 in humans, and 50% in preclinical studies). Tofacitinib had an opposite effect in animal versus human studies regarding B-cells (reduction versus increment of about 30% in humans). See table 109 and figure 11 below. The levels of lymphocyte subsets CD3+, NK and B-cells in tofacitinib treated RA patients were broadly within the range as reported for the general population, and not near the abnormal levels as reported for SCID patients with congenital lack of JAK-3 activity. See figure 9 and table 110 below.

Table 109: Changes in Lymphocyte Subsets with Tofacitinib Treatment in Rats, Monkeys, and RA Patients

Study Number	Species (n/dose group)	Dosing Phase (months)	Dose (Exposure Margin)[a]	CD3+ Total T cells[b]	CD4+ T cells[b]	CD8+ T cells[b]	B cells[b]	NK cells[b]
77435	Rat (27)	6	1 mg/kg/day (1.26)	-21.2	-14.9	-32.9	-30.9	-50.9
2003-0301	Monkey (8)	9	2 mg/kg/day (1.06)	-32.5	-32.5	-30.5	-14.5	-50.5
A3921019	RA Patients (59)	1.5	5 mg BID (NA)	-4	0	0	+29	-22
A3921025	RA Patients (51-54)	6	5 mg BID (NA)	-4.5	NA	NA	+34	-21
A3921035	RA Patients (18)	6	5 mg BID (NA)	-6	-7.5	-5	+5	-40.5

NA = Not applicable; BID = Twice daily; NK = Natural killer; CD = Cluster of differentiation; RA = Rheumatoid arthritis; n = number of animals or RA patients.
[a]Exposure margin = Unbound exposure margin, calculated by using the human unbound AUC(0-24) of 321 ng•h/mL at a dose of 5 mg BID.
[b]Values are the median percent change from vehicle control for the 6-month rat study (Week 26 of 6-month study). Median percent change from baseline are indicated in the monkey study (Week 26 of the 39-week study) and at the end of the dosing phase for studies in RA patients. CD4+ and CD8+ T cells were not evaluated in Study A3921025.

Figure 9 **Lymphocyte Subset Counts in Tofacitinib-Treated RA Patients and Healthy Adults**



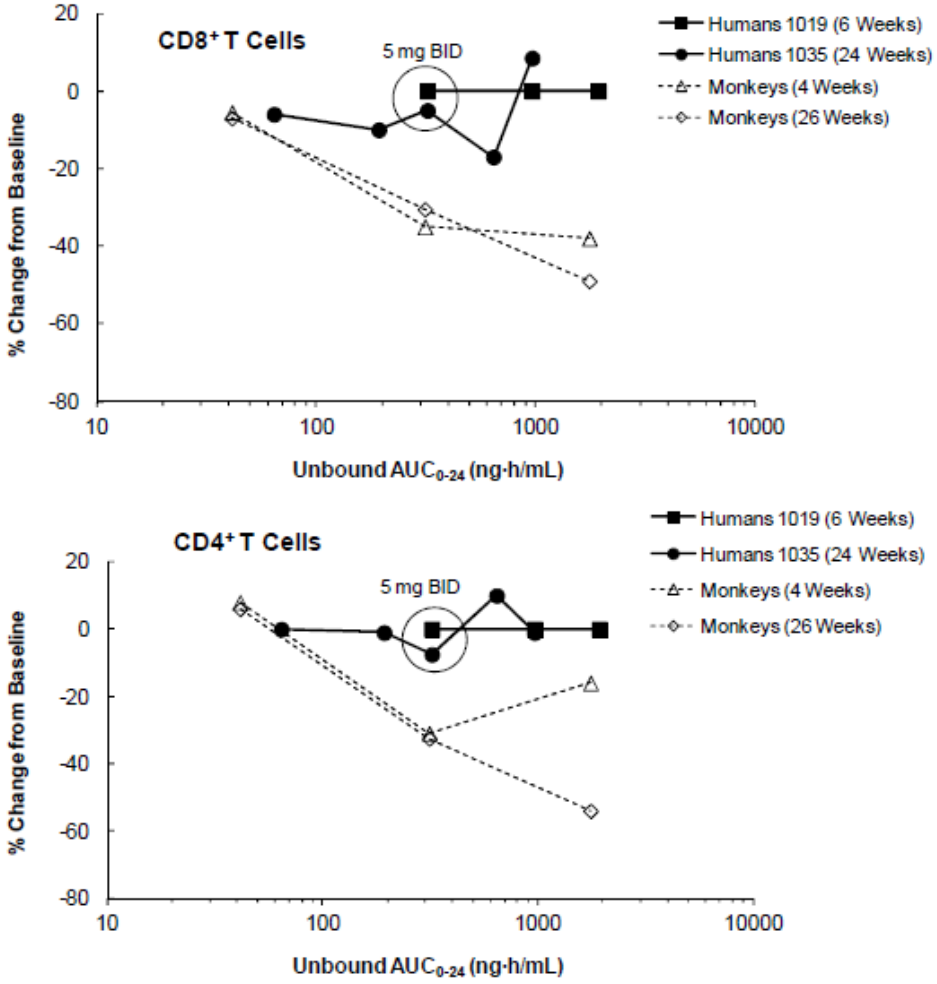
Median pretreatment baseline (BL) counts from tofacitinib naïve RA patients are compared against counts from patients treated with tofacitinib (median 22 months) (5 and 95 percentiles). The number of subjects evaluated at pretreatment BL was 774-784 for total T cells, B cells and NK cells and 419 for CD4+ and CD8+ T cells. After long term tofacitinib treatment, 151 subjects were evaluated for each of the subsets. References ranges for healthy adults show the median and 5 and 95 percentiles and 2.5 and 97.5 percentiles for healthy adults from Germany (Jentsch-Ullrich et al, 2005) and Switzerland (Bisset et al, 2004), respectively.

Table 110. Lymphocyte Subset Counts in Tofacitinib Treated Patients are Different from JAK3 SCID Patients

Parameter	Pre-treatment Baseline[a]	Long Term Tofacitinib[a]	JAK3 SCID Patients[b]	Control range[b]
CD3+ T cells	1247 (550,2477)	1119 (504,2122)	71	1014-5784
NK cells	135 (37,349)	141 (49,492)	21	87-1189
B cells	169 (49,486)	223 (78,516)	1715	121-1072

[a]Median cell counts at baseline before tofacitinib treatment in 3 phase 2 Studies (A3921019, A3921025, A3921035) .(5 and 95 percentiles); after a median of 22 months of tofacitinib treatment (A3921024 substudy). These values are shown in Figure 10.
[b]Mean cell counts from 6 of 7 JAK3 SCID infants reported and range of cell counts (cells/mm^3) from healthy adults (Roberts et al. 2004). One of 7 SCID patients had persistent transplacentally transferred maternal lymphocytes and was not included in calculating the mean values.
SCID = Severe Combined Immune Deficiency, CD = Cluster of differentiation,

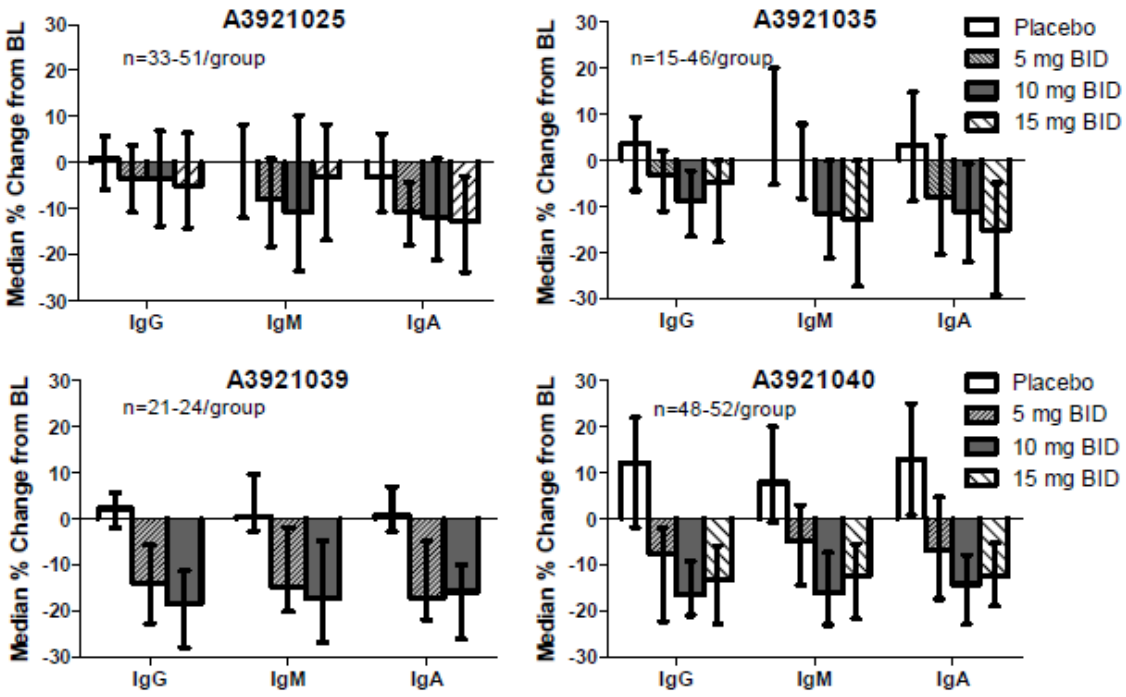
Figure 10 **CD4+ and CD8+ T cell counts in Monkeys and RA Patients at Different Exposure Levels of Tofacitinib**



BID = Twice daily; CD = Cluster of differentiation; AUC_{0-24} = Area under the concentration time curve from 0 to 24 hours postdose; RA = Rheumatoid arthritis, 1019 = Study A3921019, 1035 = Study A3921035
$CD8^+$ (upper panel) and $CD4^+$ (lower panel) T cells ($CD3^+$) were measured in clinical Study A3921019 at 6 weeks (5, 15, and 30 mg BID), in clinical Study A3921035 at 24 weeks (1, 3, 5, 10, and 15 mg BID), and for combined males and females (4/sex/dose level) in the chronic adult monkey study (2003-0301) at 4 and 26 weeks (0.5, 2, and 10 mg/kg/day). Median unbound AUC(0-24) values are 2 times the population modeled AUC(0-12) for the clinical studies, and the medians from individual values determined on Day 107 in the monkey study. Unbound AUC(0-24) was calculated as total AUC times 0.61 for humans, and times 0.65 for monkeys. $CD8^+$ and $CD4^+$ T cell counts are expressed as median percent change from baseline value.

Total serum immunoglobulins decreased by 10-20% from baseline. See Figure 11 below.

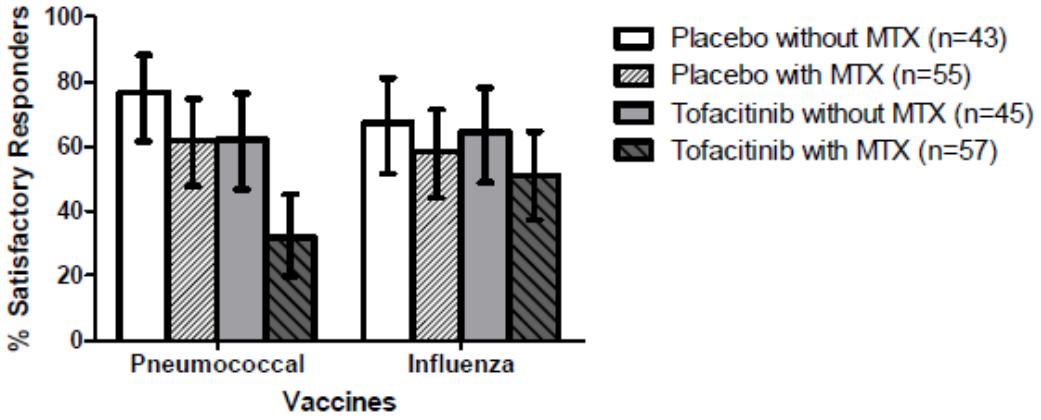
Figure 11 Changes in Total Serum IgG, IgM and IgA with Tofacitinib Treatment



Values are the median percent change from baseline (with 25 and 75 percentiles). Study A3921039 did not have a 15 mg BID group.
BL = baseline, BID = twice daily, n = number, Ig = immunoglobulin

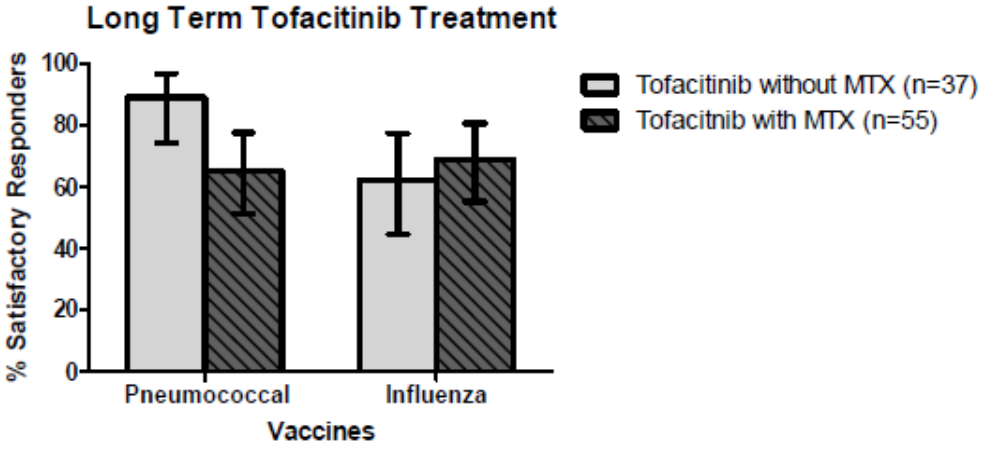
The function of immune-system was evaluated in two vaccination studies in RA patients, randomised to either tofacitinib or placebo for 29 days, with or without MTX. Another vaccination included patients after long-term tofacitinib treatment of median 22 months (see Figure 13 & 19 below).

Figure 12 **Effects of Short Term Tofacitinib Treatment on the Percentage of Patients Achieving Satisfactory Responses to Pneumococcal and Influenza Vaccines**



Error bars indicate the 95% confidence intervals.
MTX = methotrexate, n = number of patient

Figure 13 **Effect of Long Term Tofacitinib Treatment on the Percentage of Patients Achieving Satisfactory Responses to Pneumococcal and Influenza Vaccines**



Error bars indicate the 95% confidence intervals.
MTX = methotrexate, n = number of patients

Applicant's conclusions

With short term exposure, the percentage of satisfactory responders to influenza vaccine was similar between placebo and tofacitinib monotherapy groups, demonstrating preservation of humoral immune function. The pneumococcal vaccine response was decreased in patients receiving either tofacitinib alone or MTX alone in comparison to placebo. Methotrexate background therapy further diminished the responses to both vaccines. These findings, at tofacitinib dosed 10 mg (twice the proposed dose) with/without MTX, are similar to findings reported for MTX, TNF inhibitors, or the combination.

After long term tofacitinib 10 mg treatment (median 22 months, with or without MTX background therapy), the responses to both vaccines were within the range of responses observed in the placebo-treated patients from Study A3921129.

Overall, RA patients immunized after four weeks of treatment with tofacitinib monotherapy appeared to have a nominally diminished response to pneumococcal but not to influenza vaccines. A consistent decrease in immune response was apparent with background methotrexate treatment. However, antibody response to both vaccines appeared relatively unaffected when administered after longer-term treatment with tofacitinib, either as monotherapy or with background methotrexate. These data support that long term tofacitinib treatment does not have a major effect on B cell and T cell function required for humoral immune responses to vaccines.

Pharmacodynamic Reversibility

When discontinuation of tofacitinib is necessary, there is clear evidence of reversibility of pharmacodynamic (PD) effects within 14 days.

Table 111. Reversibility of Pharmacodynamic Endpoints After Tofacitinib Treatment is Discontinued

Study	Tofacitinib Dose (mg twice daily)	Tofacitinib Treatment Duration	Endpoints	Time to Evidence of Reversibility (Degree of Reversibility)	Source Tables
A3921073[b]	10	4 weeks	pSTAT5	1 day (Complete)	14.2.8.2.1
			IP-10	1 week (Complete)	14.2.2.8.1
A3921019	5, 15, 30	6 weeks	NK cells	2 weeks (Complete)	13.5.5.1
			B cells	2 weeks (Complete)	13.5.6.1
			CRP	2 weeks (Partial)	PMAR-00223, Figure 2
			Neutrophils	4 weeks (Partial)	13.7.7.4
A3921047[c]	2, 5, 15	12 weeks	LDL Cholesterol	2 weeks (Complete)	13.7.9.3.1
A3921024	10	22 months[a]	B cells	1 week (NA)	14.3.4.1.20.1
			CRP	1 week (NA)	14.2.1.1.2
			DAS28-4 (ESR)	1 week (NA)	14.2.3.1.2
			HAQ-DI	2 weeks (NA)	14.2.2.1.2

pSTAT5 = phosphorylated STAT5; IP-10 = Interferon inducible protein 10; NK cells = Natural killer cells; CRP = C-reactive protein; DAS28-4(ESR) = 28 Joint Disease Activity Score with erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire Disability Index; NA = not assessed since a baseline (pre-tofacitinib treatment) value was not determined.

[a]Median number of months of tofacitinib treatment before patients entered the A3921024 Vaccine Substudy

[b]Study A3921073 (A3921073 CSR) is a Phase 2A exploratory, placebo controlled study that evaluated PD endpoints in active RA patients (15 subjects per group) treated with tofacitinib or placebo for a 4 week period. To evaluate the recovery of PD endpoints after tofacitinib treatment was stopped, samples were collected 1 day and 1 week after the last dose on Day 28.

[c] Study A3921047 is a Phase 2 study in psoriasis patients (A3921047 CSR)

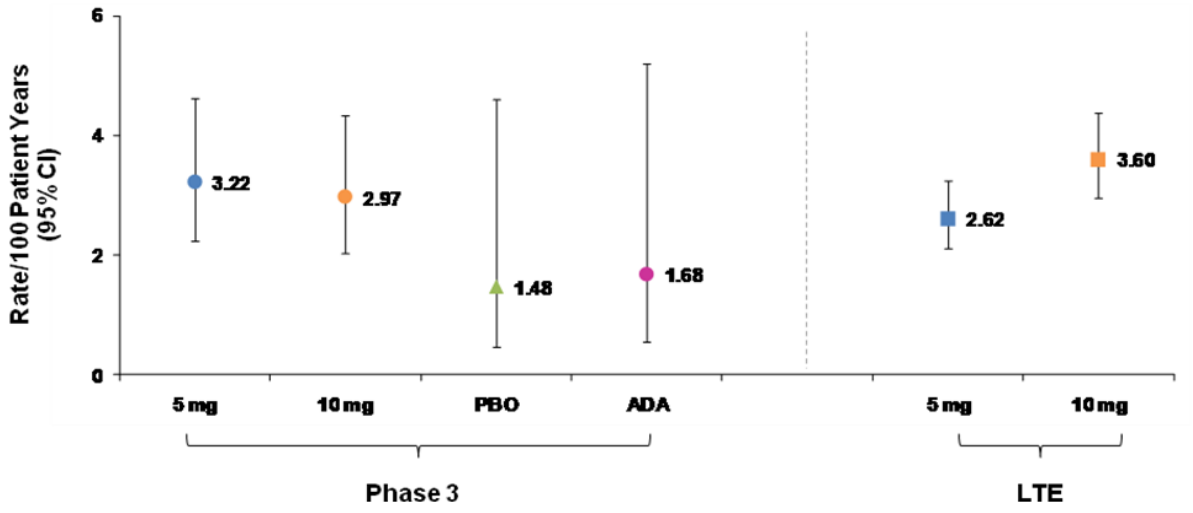
Serious and Opportunistic infections, clinical data:

Incidence rates (IRs) for serious infections (requiring hospitalization or parenteral antibiotics) are presented in Figure . The rates for serious infections have been consistent across studies at approximately 3 events per 100 patient-years. Similar rates were observed in the proposed 3rd line population with the 5 mg dose group. Somewhat higher rates were reported at the 10 mg dose in the LTE studies.

The most common serious infection was pneumonia; other commonly reported infections included skin and soft tissue infections, as are typical of an RA clinical trial population.

In the tofacitinib RA development program, 10 of 45 deaths were assessed as due to infection. For comparison, at a similar stage of development, tocilizumab similarly reported 50 deaths with 10 due to infection (Actemra FDA Summary Basis of Approval: medical Review). Mortality studies consistently show an increase in deaths due to infection in RA patients with the proportion varying widely (Myllykangas-Luosujärvi et al, 1995; Thyagarajan et al, 2012; Sihvonen et al, 2004; Guedes et al, 1999; Bjornadal et al, 2002). Difficulty in ascertainment of infection as a cause of death has been noted by multiple authors; higher rates may be reported when detailed case review (as is commonly available in clinical studies) is included in the methodology (Sihvonen et al, 2004; Myllykangas-Luosujärvi et al, 1995; Thyagarajan et al, 2012).

Figure 14. Serious Infection Rates, Overall Population, Phase 3 and LTE Studies



	Phase 3				LTE	
	Tofa 5mg BID	Tofa 10mg BID	Placebo	Ada	Tofa 5mg BID	Tofa 10mg BID
Patients (N)	1216	1214	681	204	1421	2681
Exposure (Pt-yr)	903.7	910.4	202.6	178.9	3243.1	2790.7
Events (n)	29	27	3	3	84	100

Data as of 19 April 2012;Bars indicate 95% confidence limits;5 mg and 10 mg refer to tofacitinib

ADA=adalimumab; BID= twice daily; CI=confidence interval; LTE=long term extension studies; PBO=placebo; Tofa= tofacitinib

In Study A3921064, which provided direct comparison of tofacitinib and adalimumab, there were 3/204 (1.47%) patients with a serious infection in the adalimumab treatment group and 7/204 (3.4%) patients on tofacitinib 5 mg, yielding an odds ratio of 2.4 (95% CI 0.53, 14.4). The confidence interval of the odds ratio is wide and includes unity, precluding a within study conclusion on comparative rates.

To contextualise the rate of serious infections with tofacitinib treatment, a random-effects meta-analysis model, a well established methodology for this type of analysis (Whitehead, 2002; Normand, 1999), was used to fit the incidence rates across the studies (Figure 15). The rate of serious infections in tofacitinib-treated patients (5 mg dose) is consistent with the rates reported in RA patients treated with approved bDMARDs. Sensitivity analyses assessing the impact of inclusion/exclusion criteria (e.g. published studies with zero incidence rate) did not impact the estimates.

Given the robust person years of exposure in this analysis but with the limits of making direct comparisons from a meta-analysis, it is noted that tofacitinib treated patients have similar or lower rates of serious infections than current bDMARDs. Taken together, both the similarity in serious infection rates and the similarity in effects of serologic responses to polysaccharide pneumococcal and influenza vaccines between tofacitinib and bDMARDs demonstrate that patients treated with tofacitinib are able to effectively mount an immune response.

Figure 15. Meta-Analysis of Serious Infections in Approved Biologic DMARD Agents, Randomised Clinical Trial Data*

Drug	Number of Trials	Serious Infections Rate / 100 PYO (95% CI)	Patients	PYO
Abatacept	10	3.1	5635	5752
Rituximab	6	3.62	1920	1287
Tocilizumab	10	6.29	3516	2473
Infliximab	10	6.08	4577	3546
Etanercept	7	3.3	2213	3103
Certolizumab pegol	3	6.23	1384	889
Golimumab	6	5.31	2820	1648
Adalimumab	8	4.9	2335	1913
TNF alpha inhibitor	42	4.9	20785	23988
Tofacitinib 5 mg P3ALL	5	3.22	1216	901
Tofacitinib 5 mg LTE	2	2.62	1421	3210
Adalimumab (A3921064)	1	1.68	204	179

Tofacitinib data as of 19 April 2012.;* Clinical trial data published between 1999 and 2012; The TNF alpha inhibitor row summarises all TNFi trials.

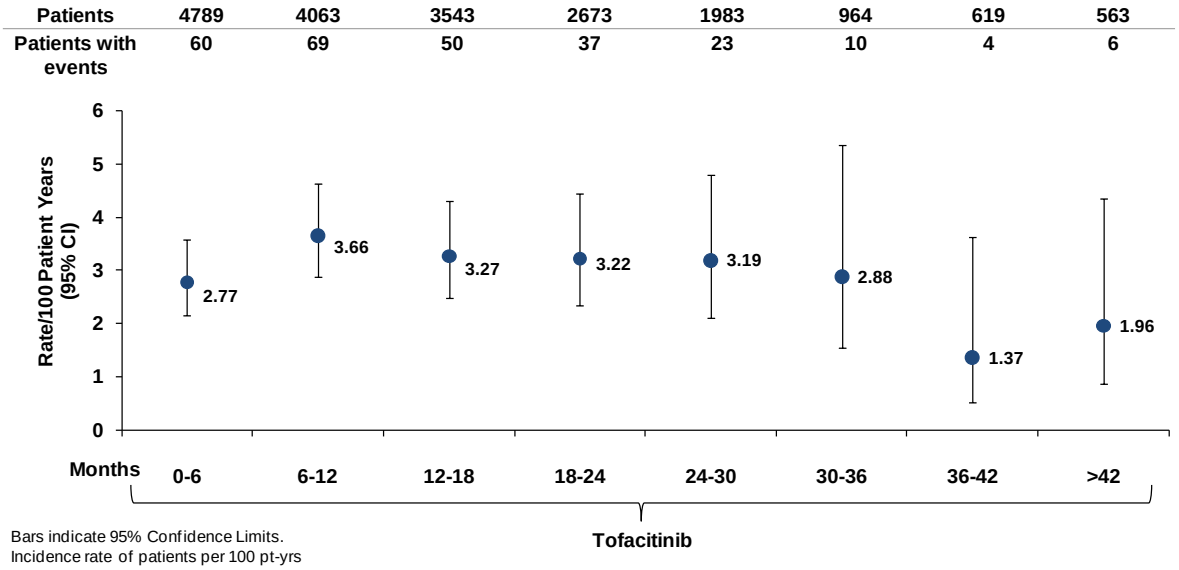
The total in this row is higher than the number (34) obtained by adding the number of trials in the figure because some studies did not report the specific TNFi studied.

CI=confidence interval; DMARD=disease modifying antirheumatic drug; LTE=long term extension studies;

P3ALL=tofacitinib Phase 3 studies; PYO=patient years of observation; Reference: Ahadieh et al, 2012.

There is no apparent increase in serious infection rates over time, as shown in Figure 16, where serious infection rates by 6 month intervals up to >42 monts in the P2P3LTE population are depicted.

Figure 16. Serious Infections Rates over Time, P2P3LTE



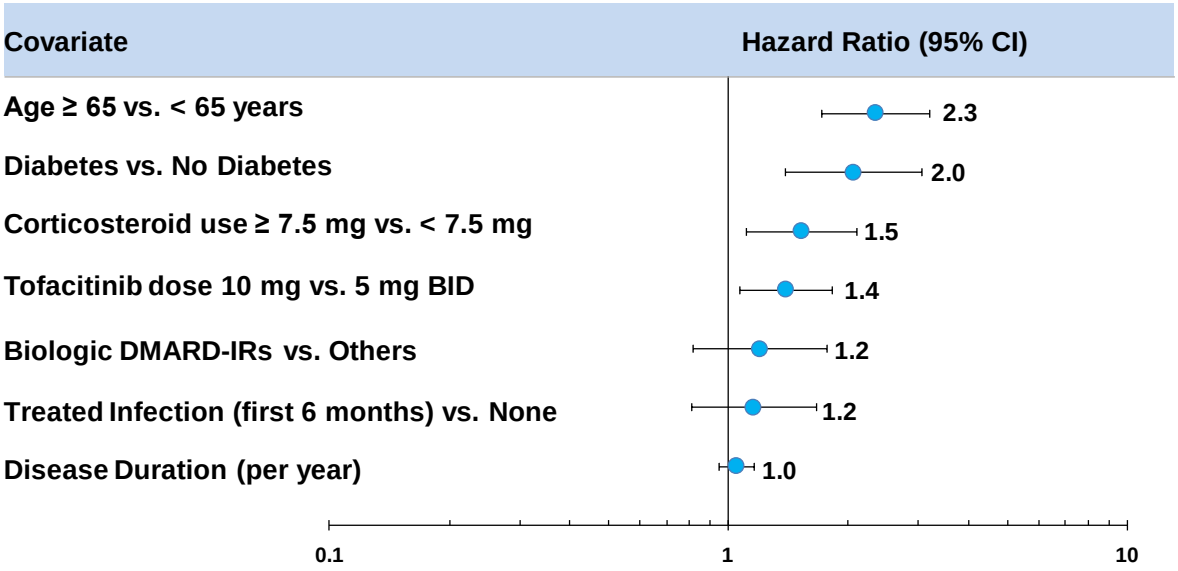
Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Phase 2, Phase 3 and LTE data as of 19 April 2012

The Applicant acknowledges that there are limitations in the interpretation of both internal (size and duration) and external (comparisons across studies, potential population differences and publication bias) comparative data. The applicant will continue to monitor and assess the rates of serious infection in the ongoing and future studies. Future assessments will include registry studies and a large RCST with a TNF inhibitor (adalimumab) as a direct comparator.

Factors Associated with Increased Risk of Serious Infections

Subpopulations of patients receiving tofacitinib were analysed to identify factors that were associated with an increased risk of serious infection. The identified factors included age, diabetes, corticosteroid dose, and tofacitinib dose (Figure 17).

Figure 17. Hazard Ratios for Serious Infections in Selected Patient Subpopulations, Cox Proportional Hazards Model



Data as of 29 Sept 2011; Post-hoc analysis of tofacitinib-treated patients; BID=twice daily; CI=confidence intervals

A caveat around interpretation of dose dependency of serious infection is the lesser exposure to 10 mg dose compared to the 5 mg dose in the long-term extension studies (LTEs). Patients who completed Phase 2 studies started LTE on 5 mg, while patients outside China and Japan who completed Phase 3 studies started LTE on 10 mg. This should be kept in mind when interpreting the differences between doses in the LTE studies.

There are no interactions between tofacitinib dose and the other identified risk factors, suggesting that these risks are likely due to underlying characteristics of the RA population. Consistent with this hypothesis, other than tofacitinib dose, these associations (age, diabetes, and corticosteroid dose) have been reported in multiple RA patient databases (Listing et al, 2013), including European registries of TNF inhibitors and other biologic DMARDs. They should therefore be familiar to practicing rheumatologists. In addition, relative to 2nd line patients, 3rd line patients showed a hazard ratio of 1.2 (95% CI: 0.81, 1.76), supporting translatability of analyses and conclusions across populations.

Appropriate risk mitigation measures based on these analyses have been proposed.

Tuberculosis

Background

Tuberculosis is caused by Mycobacterium tuberculosis, a pathogenic gram positive bacterium. Although TB is often referred to as an OI, TB occurs in immunocompetent as well as immunocompromised individuals. A minority of individuals who become infected with M. tuberculosis develop active disease and the nature of the disease is largely dependent on the competence of the host's immune system. Most commonly, TB infection involves the lungs (80%); the proclivity for extrapulmonary spread of TB is determined by immunocompetence (Bieber et al, 2004).

The incidence of TB among RA patients has been primarily documented in the drug safety literature, particularly since the advent of TNF inhibitor treatments. There are abundant data on the incidence of TB in RA populations from registry analyses published in the literature, with a majority of publications addressing the risk of TB in those treated with TNF inhibitor therapies. However, published data from

clinical trials are more limited than registry data.

Differential risks for TB associated with biologic agents used to treat RA have been reported and patients treated with these agents appear to be at increased risk for TB compared to the general population (Askling et al, 2005). Additionally, a higher proportion of TB infections in RA patients treated with biologic agents are extrapulmonary/miliary; extrapulmonary involvement has been reported in 50%, 45% and 40% of TB cases with etanercept, infliximab and adalimumab, respectively (Bieber et al, 2004).

The incidence rate of TB varies geographically with most cases occurring in Asia (59%); China and India combined accounted for 38% of cases worldwide (WHO, 2011). Depending on geographic location, the annual incidence of TB can vary from 0 to more than 300 cases per 100,000 people (WHO, 2011). Thus, interpretation of the TB incidence rate is highly dependent on the geographic region(s) where the data originated.

TB in the Tofacitinib RA Development Program

The tofacitinib development program was conducted globally and included many countries with high endemic TB rates.

Tuberculosis was reported in 16 tofacitinib treated patients. Twelve (12) of these patients lived in countries with high endemic TB rates and may therefore have been newly infected while on tofacitinib therapy. One tofacitinib-treated (10 mg dose) patient who lived in Europe (Spain) developed TB and recovered with appropriate therapies.

To contextualise the rate of TB in the tofacitinib RA program, the geographic distribution of tofacitinib TB incidence rates, and corresponding regional TB incidence rates are shown in Table 112.

Table 112. Tuberculosis Rates for Tofacitinib Patients by Country Background Incidence Rates, Phase 2, 3, and Long Term Extension Studies

Country Background IR* (events/100 pt-yrs) [Country from tofa RA program]	**Tofacitinib Incidence Rate** (95% CI)	**Published IRs in RA Patients Treated with Biologics**
Low (≤ 0.01) [United States]	0.030 (0.004, 0.212)	0.024-0.257
Intermediate (≥ 0.01 and ≤ 0.05) [Mexico, Spain, Japan]	0.086 (0.028, 0.265)	0.039-0.449
High (> 0.05) [China, India, Korea, the Philippines, Thailand]	0.748 (0.425, 1.317)	2.558 (Korea)

Country Background IR* (events/100 pt-yrs) [Country from tofa RA program]	Tofacitinib Incidence Rate (95% CI)	Published IRs in RA Patients Treated with Biologics

Data as of 19 April 2012

* TB background country incidence rate categories from World Health Organization, 2011 report for year 2010.

The tofacitinib TB rate in the low incidence countries (1 case) was hand calculated because the event occurred after the patient was off study drug for 2 months and therefore the event is not in the study database.

CI=confidence interval; IR=incidence rate; pt-yrs=patient years; TB=tuberculosis; tofa=tofacitinib

Keane et al, 2001; Carmona et al, 2003; Wolfe et al, 2004; Askling et al, 2005; Yamada et al, 2006; Seong et al, 2007; Brassard et al, 2006; Burmester et al, 2007; Baldin et al, 2005; Sichletidis et al, 2006

Infection with TB was pulmonary in 10 of these 16 patients and included extra-pulmonary involvement in the remaining 6 patients. Thus, the proportion of 38% of extrapulmonary/miliary TB in tofacitinib treated patients is similar to the proportions reported with biologic agents as described above (Bieber et al, 2004). There were no deaths due to TB reported.

Applicant's summary of TB

The incidence rates of TB observed in tofacitinib treated RA patients are reflective of the expected rates based on underlying geographic risk of infection, given the global nature of the development program and the countries in which TB cases were reported.

Opportunistic Infections

Opportunistic infections are caused by bacterial, viral, fungal or protozoan organisms that typically do not cause disease in a healthy host. These are frequently but not always commensal organisms; the list of infections that are considered OI varies considerably. Persons with compromised immune systems, such as those with RA and other autoimmune disorders and/or treated with immunomodulatory treatments, are more vulnerable to opportunistic infections.

The majority of the literature addressing the incidence of OIs among persons with RA examines occurrence in the context of specific RA treatments like MTX and TNF inhibitor therapies (Cunnane et al, 2003). Data from clinical trials is sparse, likely due to patient characteristics at enrollment (i.e., screening procedures excluding "at risk" populations) and limited follow-up periods. In this setting, it is difficult to distinguish between the risk factors that result from inflammatory diseases (e.g., severity of inflammation, reduced functional capacity, and co-morbid conditions) and the risk arising from treatment with immunosuppressive therapies (Raychaudhuri et al, 2009).

Among the serious infections or adverse events, OIs are relatively rare (Wolfe et al, 2006-2). OIs in the RA literature are generally addressed in the context of safety outcomes and adverse events in drug trials and are seldom distinguished from serious infections or other general adverse events and addressed explicitly.

Rates of OI are difficult to compare across studies of other RA therapies due to differences in geographic prevalence of some OI and, importantly, the different definitions of OI that are used in the literature. For example, TB is sometimes included in rates of OI and sometimes it is not. Herpes zoster is often not considered an OI except when disseminated or multidermatomal; however, rates of

uncomplicated ‘shingles’ are sometimes included in overall OI rates.

In the tofacitinib RA development program, OIs were infrequent (Table 113) as discussed below. When available, discussion of comparative data for other RA therapies is included.

Table 113. Opportunistic Infections

	Number of Patients (n)		
	Whole Population	**European Union Only**	**European Union 5 mg Dose Only**
Oesophageal candidiasis	8		
Cytomegalivirus	6	1	
Cryptococcus	3		
Pneumocystis pneumonia	3		
Multidermatomal herpes zoster	2	2	1
Non-TB mycobacteria	2		
BK encephalitis	1		

Whole population: tofacitinib P2P3LTE all doses; EU only: patients in EU, all tofacitinib doses.

Data as of 19 April 2012

n=number of patients experiencing opportunistic infections;

Infections classified as opportunistic that were reported in patients treated with tofacitinib included oesophageal candidiasis, cytomegalovirus (CMV), cryptococcosis, pneumocystis pneumonia, multidermatomal herpes zoster, non tuberculosis mycobacteria, and BK virus encephalitis.

Additional details of these OI cases are provided below (Table 114):

Table 114. Details of Opportunistic Infections in Tofacitinib P2P3LTE Studies

Oesophageal candiasis	8 Cases • Five of 8 cases of oesophageal candidiasis were incidental findings during upper endoscopies • A single case, assessed as mild by the Principal Investigator, resulted in permanent discontinuation from study.
Cytomegalovirus	6 cases of viremia/infection • CMV antigenemia without evidence of end organ involvement , which resolved with discontinuation of tofacitinib and administration of anti-viral therapy.

	• CMV found in association with an esophageal ulcer which resolved without antiviral therapy while tofacitinib treatment was continued • CMV sialoadenitis shown on biopsy which resolved with discontinuation of tofacitinib and administration of anti-viral therapy . • CMV hepatitis diagnosed by increased transaminases in the setting of CMV antigenemia, which resolved with discontinuation of tofacitinib and administration of anti-viral therapy • CMV chorioretinitis which resolved with discontinuation of tofacitinib and administration of anti-viral therapy . • CMV pneumonitis in association with bacterial pneumonia, which resolved with discontinuation of tofacitinib and administration of anti-viral therapy .
Cryptococcosis	3 cases • Cryptococcal pneumonia (2 cases), improved with appropriate medical management • Cryptococcal meningitis, resolved
Pneumocystis pneumonia	3 cases • Two (2) cases of Pneumocystis jirovecii pneumonia cases occurred in Japan, a country where pneumocystis is diagnosed 10 times more frequently than in the EU.* An additional case was diagnosed in Chile . One death occurred in a Japanese female patient.
Multidermatomal herpes zoster	2 cases • Resolved with discontinuation of tofacitinib and appropriate antiviral therapy
Nontuberculosis mycobacteria	2 cases • Both cases of nontuberculosis mycobacterial lung infections occurred in Japan.
BK encephalitis	1 case • BK encephalitis was diagnosed in a critically ill patient with septic arthritis based on a positive polymerase chain reaction (PCR) test result for BK virus in cerebrospinal fluid; the patient improved with appropriate medical therapy.

*Takeuchi and Kameda, 2010

Oesophageal candidiasis, cryotococcosis, pneumocystocis, multidermatomal or disseminated herpes zoster and non tuberculous mycobacteria have all been reported in RA patients; however, it is not possible to provide a meaningful or accurate comparison of the relative frequency of reporting across the different RA therapies and tofacitinib. Uncomplicated herpes zoster is usually not considered an OI. Candidiasis is typically considered an OI only when there is evidence of invasive disease; as described above most cases of oesophageal candidiasis reported in tofacitinib treated patients were incidental

findings on endoscopies performed for other reasons. There was no evidence of invasive disease.

CMV has been reported infrequently in RA patients (Ramey et al, 1999; Kim et al, 1996, Thomas et al, 1997; Clerc et al, 1991; Belin et al, 2003), and disease associated with BK virus is rare although neurologic disease associated with this virus has been reported in immunocompromised patients (Friedman et al, 2006).

Because of the complex relationship of host and organism for many agents that may cause OI, simple identification or isolation of an organism is often not sufficient to make a definitive determination of an OI. To ensure that OIs are being properly identified, assessed and reported, a committee of infectious disease experts was established in February 2013 to adjudicate all potential OIs reported in tofacitinib clinical studies.

Applicant's Summary of OI

Opportunistic infections were uncommon in countries within the European Union, and only one was reported at the 5 mg dose: a patient in Finland was hospitalised for multidermatomal herpes zoster and made a complete recovery with treatment.

Tuberculosis infections were distributed geographically as expected, and cases of other opportunistic infections were generally similar to those reported in the RA population undergoing immunosuppressive therapy. Given the geographic distribution of tuberculosis and rare occurrence of other opportunistic infections with variable case definitions, the rates of opportunistic infection are difficult to compare across studies of other RA therapies. The Applicant will continue to monitor and assess the risk of TB and OI in ongoing and future studies, with adjudication by an expert committee.

Lymphocyte Counts and Infections

Lymphocyte counts below 500/mm^3 were uncommon (0.2% in the Phase 3 studies and 0.4% in the LTE studies), but were associated with an increased incidence of serious infections in tofacitinib treated patients (Table 115 A).

OIs are uncommon, with one event occurring in a patient with a confirmed lymphocyte count of <500/mm^3 (Table 115 B).

Table 115. Lymphocyte Counts and Serious Infections (A) / Opportunistic Infections (B), Tofacitinib 5 mg Patients, LTE Studies

A

	Tofacitinib 5 mg BID		
Confirmed Absolute Lymphocyte Count (x 1000/mm^3)	N	Serious Infections	
		n	%
≥2.0	168	13	7.7
≥1.5 - <2.0	290	17	5.9
≥1.0 - <1.5	612	31	5.1
≥0.5 - <1.0	339	21	6.2
<0.5	9	2	22.2
Total	1418	84	5.9

B

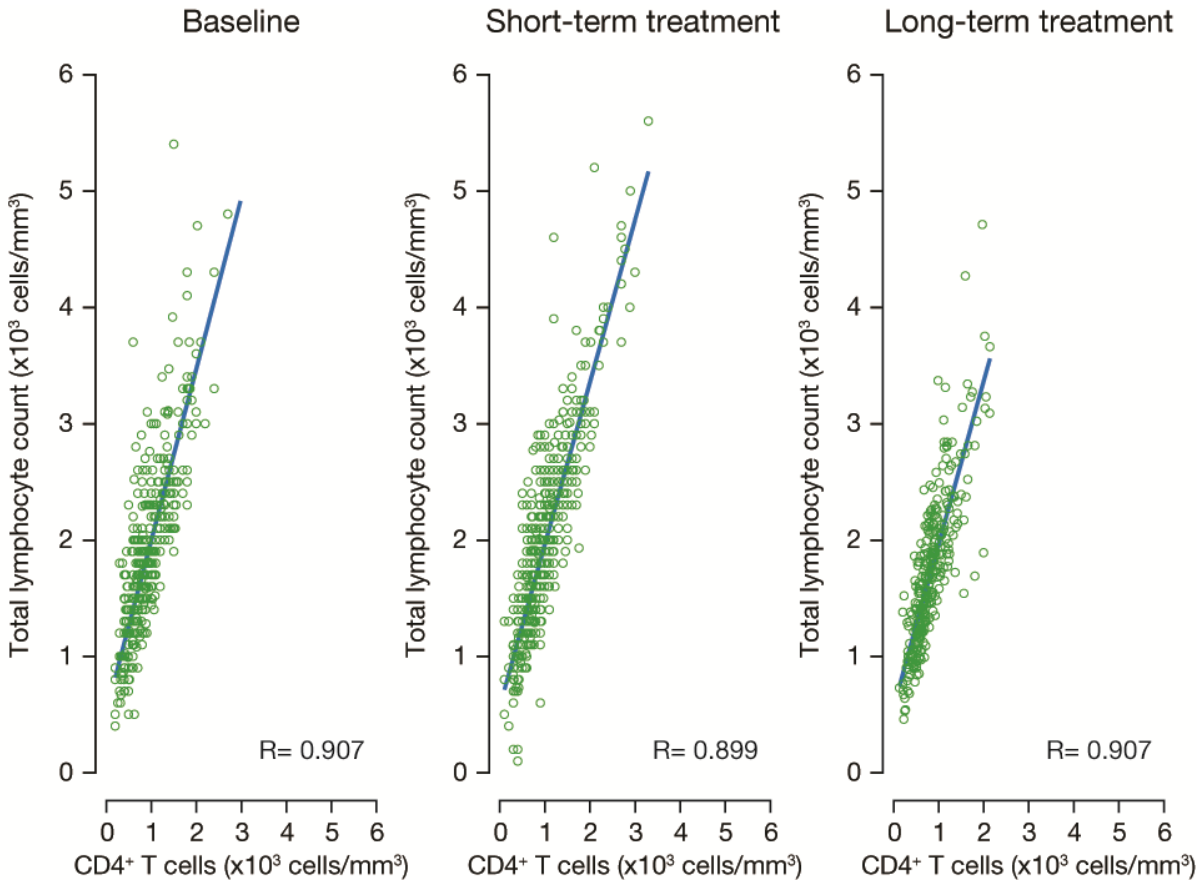
	Tofacitinib 5 mg BID		
Confirmed Absolute Lymphocyte Count (x 1000/mm^3)	N	Opportunistic Infections	
		n	%
≥2.0	168	1	0.6
≥1.5 - <2.0	290	3	1.0
≥1.0 - <1.5	612	3	0.5
≥0.5 - <1.0	339	5	1.5
<0.5	9	1	11.1
Total	1418	13	0.9

Data as of 19 April 2012, LTE studies

LTE = long-term extension, BID = twice daily, N = number of patients with the confirmed lymphocyte count, n = number of patient with infection

Lymphocyte subset data were collected in 500-1300 patients in Phase 2 studies. There was a high degree of correlation observed between absolute lymphocyte counts and CD4+ T cell counts (Figure 18), indicating that evaluation of lymphocyte subset levels do not add information beyond that provided by total lymphocyte counts. Similar correlation was observed with CD8+ T cells. The Applicant is committed to confirming these results by conducting additional lymphocyte subset analyses in the LTE studies post approval (see Part VII, Annex 6 in the RMP).

Figure 18. Correlation between Absolute Lymphocyte and CD4+ T Cell Counts



Open circles are individual patient data; solid lines represent prediction from linear regression; R denotes pearson's correlation coefficient; baseline (n=458) and short term (n=403) treatment data were derived from Phase 2 Studies A3921019 and A3921035; short term treatment data (middle panel) are values at the end of treatment (6 weeks for Study A3921019 and 24 weeks for Study A3921025); long term data (n=169) were derived from the Study A3921024 vaccine substudy.

Herpes Zoster

The overall incidence rate for herpes zoster in the Phase 3 studies was 4.4 events per 100 patient-years (95% CI 3.21, 6.01) in tofacitinib 5 mg treated patients, which was 1.6-fold higher than the Phase 3 adalimumab rate (2.8 [95% CI 1.17, 6.76]) as well as higher than rates typically reported for other RA therapies. The majority of patients (89.7% [35/39] in Phase 3 studies at 5 mg) did not require permanent discontinuation from study drug and all responded to appropriate medical treatment. In addition, the proportion of patients receiving tofacitinib 5 mg with serious or multidermatomal herpes zoster was small (4/39 were serious and 1/39 were multidermatomal), and consistent with published rates (Strangfeld et al, 2009). The data for the 10 mg dose are similar.

Infection Risk Management Strategy

Risk Minimisation - SmPC

To address the CHMP concerns related to the risk of serious infections, a posology of tofacitinib 5 mg twice daily only is being proposed by he applicant for the SmPC. Specific information for the identified risk factors of age, diabetes and use with concomitant corticosteroids of ≥ 7.5 mg per/day is provided in the Special Warnings and Precautions section of the SmPC. The association of significant lymphopenia with an increased incidence of serious and opportunistic infections is provided in the proposed SmPC to enable tofacitinib to be used safely and effectively.

Monitoring of lymphocyte levels at baseline and every 3 months during treatment is recommended. Tofacitinib treatment should not be initiated in patients with absolute lymphocyte counts <500/ mm^3. Health professionals are provided with precautions for use including advice that patients with a confirmed lymphocyte count of <1000/mm^3 should be monitored more frequently for clinical and laboratory signs of infection, and patients with a confirmed lymphocyte count <500/mm^3 should be discontinued from tofacitinib therapy.

The proposed SmPC further addresses the risk of infections by advising prescribers that tofacitinib treatment must not be initiated in patients with active tuberculosis (TB) or other serious infections such as sepsis or opportunistic infections. Tofacitinib should be interrupted if a serious infection occurs. Descriptions of the types of infections that have been observed in patients treated with tofacitinib and guidance on appropriate patient selection, including pre-treatment testing (e.g. for TB and for hepatitis), and management of factors that may put patients at greater risk of infection are included.

Risk Minimisation – Educational PlanThe guidance for prescribers in the proposed SmPC will be further communicated through an educational programme directed at both patients and healthcare providers. These include a patient alert card, a HCP prescribing brochure, HCP educational slides, and HCP treatment intiation and maintenance checklists as risk minimisation tools. The effectiveness of risk minimisation will be assessed through surveys and registries under 'real world' conditions of use.

Risk Assessment

Opportunistic infections are a key focus of the large, RCST. This study will evaluate the type and incidence of OI in a large number of tofacitinib treated patients over a long period, and allows for direct comparison with a cohort of patients treated with a TNF inhibitor (adalimumab). Incidence rates of tuberculosis in RA clinical trials depend largely on the underlying risk of infection and pre-entry screening. OIs other than TB in clinical trials of RA patients are rare and given the variability in diagnostic methodologies, as well as the lack of uniformly applied case definitions, this limits cross study comparisons. To further study OIs, a committee of independent infectious disease experts has been established to adjudicate suspected OI occurring in ongoing and future tofacitinib RA studies. Expert adjudication will enhance the assessment of these important events and allow greater understanding of the type and incidence of OI in tofacitinib treated RA patients.

Ground 3

The overall safety profile, and the uncertainties relating to safety, are not acceptable, in particular the incidence and severity of infections, malignancies, lymphoma, gastro-intestinal perforations, hepatic enzymes elevations/drug-induced liver injury and lipids and 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 risks and their management in clinical practice, which are not offset by the benefits of treatment.

This section addresses the remaining safety areas of concern: malignancies and lymphomas, lipid increases and cardiovascular (CV) safety (Section 0), hepatic safety (Section 0), and gastrointestinal perforations (Section 0). Serious and opportunistic infections were discussed in Section 0, immediately preceding this section.

The tofacitinib RA development programme (Phase 2, Phase 3 and LTE studies) has evaluated safety in 4789 tofacitinib treated patients, including 1700 patients treated for 4000 patient-years at twice the

proposed dose. At the proposed dose of 5 mg BID, tofacitinib safety has been evaluated in nearly 2000 patients, for over 4000 patient-years of experience.

In the 3rd line population, 726 patients were treated with tofacitinib representing 853 patient-years of exposure. The data presented below demonstrate that the safety of tofacitinib is similar between the overall study population and 3rd line patients and thus the overall database is considered supportive of the proposed indication.

Malignancies and Lymphomas/Lymphoproliferative Disorders

The Applicant acknowledges that due to the typically long latency period for malignancies, extended periods of observation are required to definitively determine whether the risk of malignancy is increased. Data thus far do not indicate that RA patients treated with tofacitinib are at an increased risk of malignancy compared to other RA therapies. The Applicant is committed to continued evaluation of the risk of malignancy in current and future studies, including evaluation through EU and other registries as well as a large, long term, RCST with a primary endpoint of adjudicated malignancies.

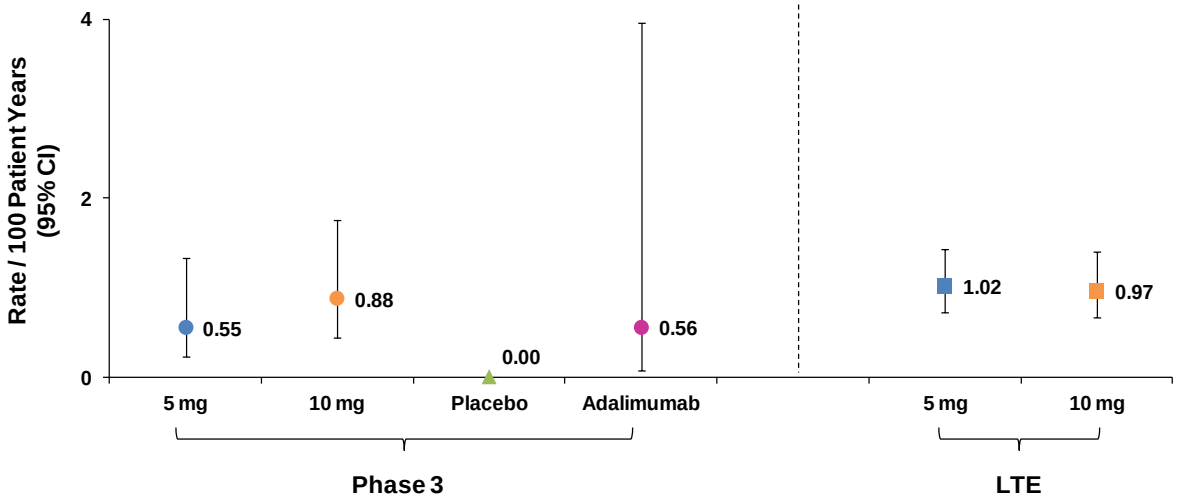
Certain types of cancers may occur at higher frequency in patients with RA, regardless of the treatment modality, including Hodgkin's and non-Hodgkin's lymphoma, leukemia, myeloma, and lung cancer (Khurana et al, 2008). In addition, malignancies, including lymphomas, are a concern with all therapeutic agents that treat RA by modulation of the immune system.

Tofacitinib is not mutagenic or genotoxic based on a series of in vitro and in vivo tests for gene mutations, chromosomal damage, and DNA damage. In nonclinical studies no treatment-related neoplasia was observed in rasH2 transgenic mice. Treatment-related tumours observed in the rat carcinogenicity study are considered to be not relevant or of low relevance to humans based on mechanism or exposure margins. These nonclinical data support the chronic use of tofacitinib for the treatment of rheumatoid arthritis.

Overall Malignancies (excluding NMSC)

Malignancies (excluding non-melanoma skin cancer [NMSC]) were infrequent in the Phase 3 and LTE studies and rates were consistent across active treatment groups (Figure 19). The overall malignancy rate (excluding NMSC) is 0.887 (95% CI: 0.707, 1.112, 19 April 2012 data cut). In Phase 3, the malignancy rates were similar between tofacitinib 5 mg and adalimumab. Aside from NMSC, there were no malignancies in placebo patients (maximum exposure to placebo was 3 to 6 months).

Figure 19. Malignancy (excl. NMSC) Rates in Active Treatment Groups, Phase 3 and LTE Studies (19 April 2012)



Tofacitinib data as of 19 April 2012.

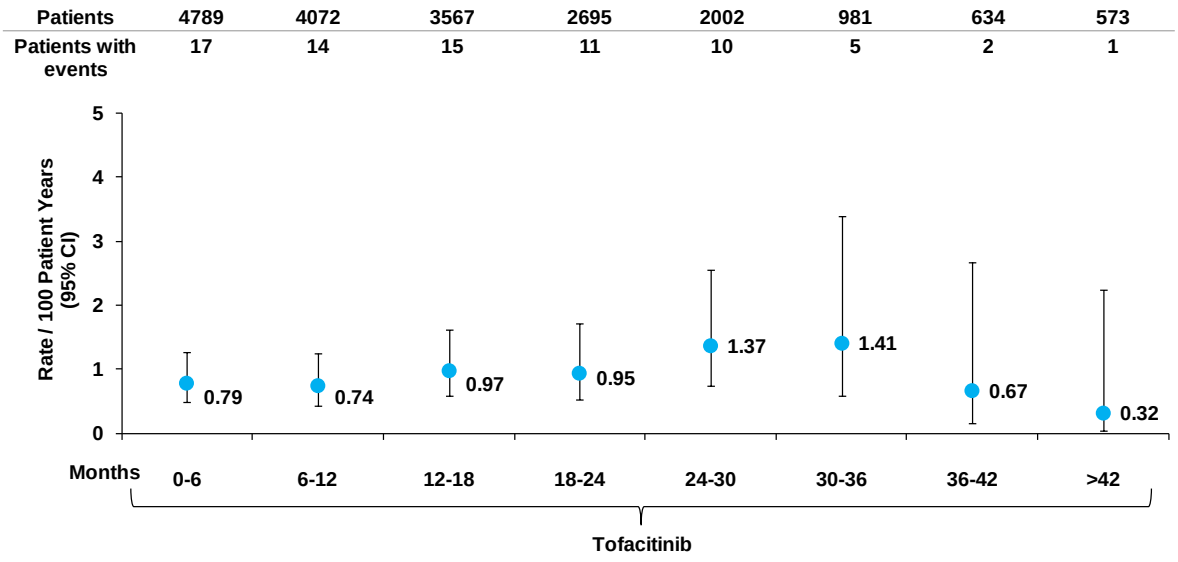
Bars indicate 95% confidence intervals 5 mg and 10 mg refers to tofacitinib

CI=confidence interval; LTE=long term extension; NMSC=nonmelanoma skin cancer;

The SIR for all malignancies (excluding NMSC) as compared with the US Surveillance Epidemiology and End Results (SEER) database is 1.12 (95% CI 0.88-1.40). These data indicate that the overall rate of malignancy is not increased compared with the general US population.

Malignancy rates during treatment with tofacitinib are presented in Figure 20 by 6 month intervals.

Figure 20. Malignancy (excl. NMSC) Rates Over Time, All Tofacitinib Patients, Phase 2, 3 and LTE Studies (19 April 2012)



Tofacitinib data as of 19 April 2012.

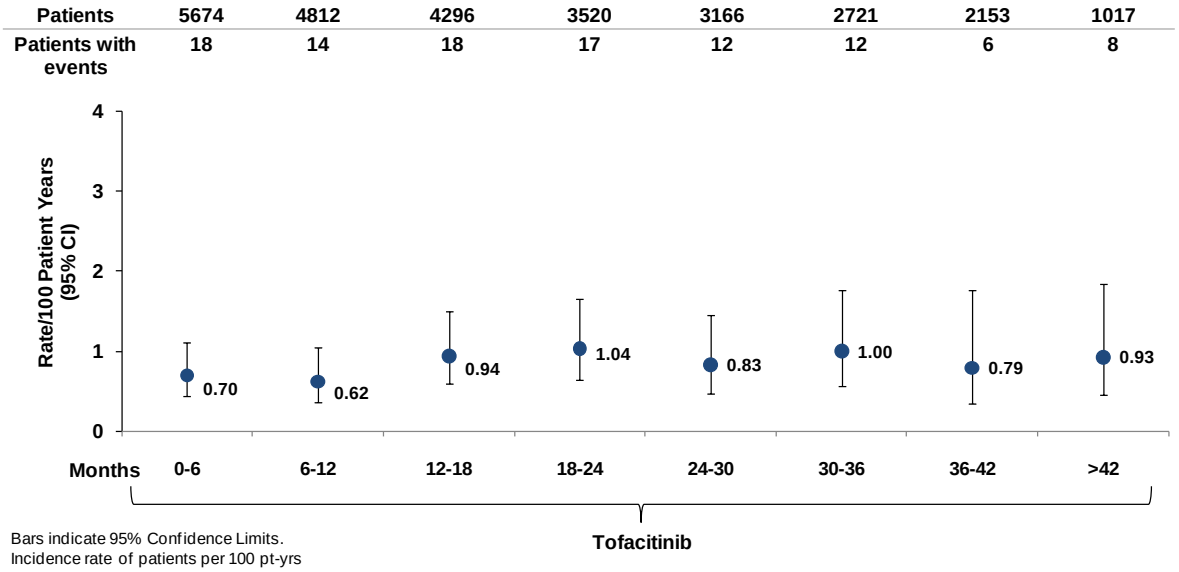
CI=confidence interval; LTE=long term extension; NMSC=nonmelanoma skin cancer

There were variation in rates over time, and CHMP has expressed concern that the measured rate of 1.37 per 100 PYO, an increase relative to earlier time intervals, might truly reflect a dependency between incidence and duration of exposure to tofacitinib.

To address this ground for refusal, the Applicant reports the rate of malignancies using a data cut off date of 10 April 2013, produced as part of ongoing safety monitoring. These data include additional patients and patient-years of treatment from more recent completed Phase 3 studies (A3921044 2-Year, A3921069 1-Year) and ongoing LTE studies. This dataset includes 5674 patients with 12669 patient-years of tofacitinib treatment, which represents an additional ~4000 patient-years of exposure. The overall malignancy rate (excluding NMSC) for these patients was 0.83 (95% CI: 0.685, 1.004), which is slightly less, but consistent with, the overall rate of malignancy in previous data cuts.

Malignancy rates for 42 months of treatment with tofacitinib by 6 month intervals for this supplemental data cut are presented by 6 month intervals (Figure 21). These data demonstrate the expected lower rate during the first 6 to 12 months of exposure due to recruitment bias, a well known phenomenon in epidemiology research (Hernan et al, 2004). Subsequent timepoints confirm that there is no increase in the rate of malignancy over time.

Figure 21. Malignancy (excl. NMSC) Rates over Time, All Tofacitinib Patients, Phase 2, 3 and LTE Studies (10 April 2013)



Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Phase 2, Phase 3 and LTE data as of 10 April 2013

NMSC = nonmelanoma skin cancer, LTE = long-term extension

To contextualise the rate of malignancies with tofacitinib treatment, a random-effects meta-analysis model, a well established methodology for this type of analysis (Whitehead, 2002; Normand, 1999), was used to fit the incidence rates across the studies (Figure 22). Malignancy rates were similar between biologic DMARDs, including TNF inhibitors, and tofacitinib. Sensitivity analyses assessing the impact of inclusion/exclusion criteria (e.g. published studies with zero incidence rate) did not impact the estimates.

Figure 22. Meta-Analysis of Malignancy (excl. NMSC) Rates in Approved Biologic DMARD Agents, Randomised Clinical Trial Data* and Tofacitinib 5 mg

Drug	Number of Trials	Malignancy Rate / 100 PYO (95% CI)	Patients	PYO
Abatacept	6	0.73	3328	3702
Rituximab	2	1.36	1020	738
Tocilizumab	8	1.06	6825	3222
Infliximab	7	1.27	1742	1908
Etanercept	8	1.03	2574	5472
Certolizumab	6	0.59	2367	4065
Golimumab	5	1.23	2227	1284
Adalimumab	12	1.24	9228	8410
TNF alpha inhibitor	38	1.1	18993	21502
Tofacitinib 5mg P3All	5	0.55	1216	904
Tofacitinib 5mg LTE	2	1.02	1421	3241
Adalimumab (A3921064)	1	0.56	204	179

Tofacitinib data as of 19 April 2012.

* Clinical trial data published between 1999 and 2012.

CI = confidence interval; DMARD = disease modifying antirheumatic drug; LTE = long term extension studies; NMSC=nonmelanoma skin cancer; P3ALL = tofacitinib Phase 3 studies; PYO = patient years of observation

Reference: Ahadieh et al, 2012.

Rates of specific cancers, such as lung and breast cancer, in the tofacitinib RA programme also appear similar to those reported for biologic DMARD therapies (Table 116). The rates and types of NMSC in tofacitinib treated patients are similar to those reported in the published literature for RA patients (data available on request).

Table 116. Incidence Rates for Lung and Breast Cancer, for Tofacitinib 5 mg Patients and Biologic DMARDs*

	Incidence Rate Tofa 5 mg BID Phase 3 n Events/100 pt-yrs (95% CI)	Incidence Rate Tofa 5 mg BID LTE n Events/100 pt-yrs (95% CI)	Incidence Rate TNF inhibitors/ Biologic DMARDs* Events/100 pt-yrs

Table 116. Incidence Rates for Lung and Breast Cancer, for Tofacitinib 5 mg Patients and Biologic DMARDs*			
	Incidence Rate **Tofa 5 mg BID** **Phase 3** **n** **Events/100 pt-yrs** **(95% CI)**	**Incidence Rate** **Tofa 5 mg BID** **LTE** **n** **Events/100 pt-yrs** **(95% CI)**	**Incidence Rate** **TNF inhibitors/** **Biologic DMARDs*** **Events/100 pt-yrs**
Lung	n=3 0.332 (0.107, 1.029)	n=4 0.123 (0.046, 0.329)	0.228-0.26[a]
Breast	*0*	*n=7* *0.260 (0.124, 0.545)*	*0.11-0.34*[a]

* IRs from randomised clinical trial data; Smitten et al, 2008; Phase 3 data as of 29 March 2011;LTE data as of 19 April 2012; CI = confidence interval; DMARD = disease modifying anti-rheumatic drug; IR = incidence rate; n = number of unique patients with event; pt-yrs = patient years

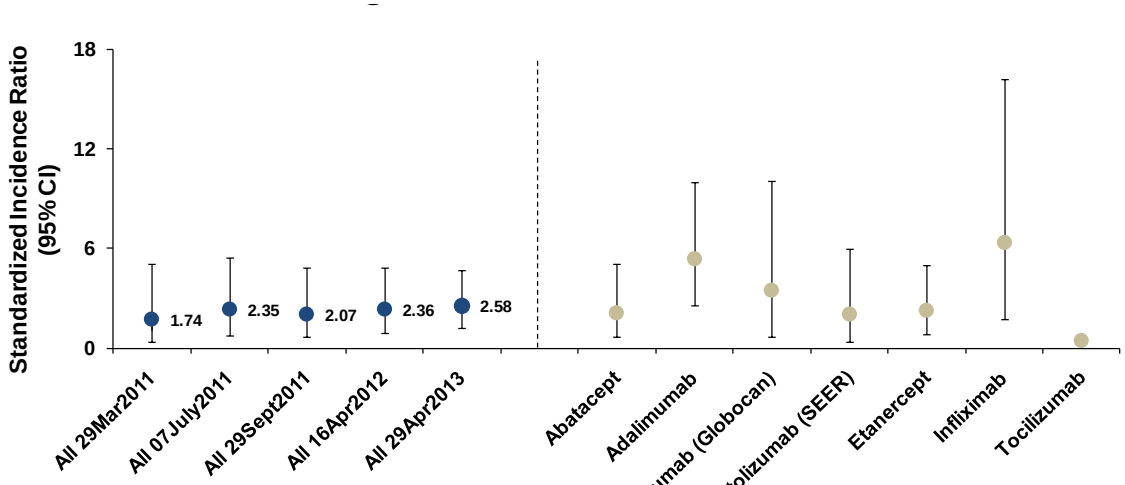
Lymphomas/Lymphoproliferative Disorders (LPD)

A total of 10 cases of lymphoma were reported for tofacitinib patients in the RA program with an estimated total of 13231 patient years of exposure, yielding an IR estimate of 0.076 events per 100 PYO, as of 10 April 2013. There were no cases of lymphoma in the placebo or adalimumab groups. There is no apparent pattern of occurrence based on either tofacitinib dose or duration of therapy. Published lymphoma IRs for RA patients treated with nonbiologic and bDMARDs range from 0.06 to 0.140 events per 100 PYO.

In the tofacitinib trials, the SIR for lymphoma, normalised for age and gender to the US general population, has ranged between 1.74 and 2.58, based on periodic monitoring during the development program, and is consistent with those reported in RA clinical trials of TNF inhibitors and other bDMARDs (

Figure 23).

Figure 23. Lymphoma Standardised Incidence Ratios for Tofacitinib During the RA Program versus Published Standardised Incidence Ratios of Biologic DMARDs



	All Mar 2011	All July 2011	All Sept 2011	All Apr 2012	All Apr 2013
Pts with events	3	5	5	7	10
Exposure (PY)	5651	6993	7977	9935	13231

Lymphoma SIR
Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Data as of 29Apr2013

To ensure all lymphoma cases were captured, the SIR for Apr 2013 is calculated from data that include the year-2 blinded data from A3921069.

RA = rheumatoid arthritis, DMARDS = disease modifying antirheumatic drugs, PY = patient-year

Occurrence of Post Transplant Lymphoproliferative Disorder/Lymphoma in Tofacitinib Renal Transplant Studies

In contrast to the lymphoma IR observations in the RA development program, an increased rate of post transplant lymphoproliferative disorder (PTLD) was observed in renal transplant patients treated with tofacitinib in transplant study A3921030 and its extension study A3921050, compared with the general renal transplant population. The overall PTLD incidence proportion was 5/218 (2.3%) which exceeds the incidence typically reported in renal transplant patients (approximately 0.5%-1%) (Caillard et al, 2005 and Caillard et al, 2006).

There are significant differences between the intensity and complexity of immunosuppressive regimens used in the tofacitinib renal transplant program and the tofacitinib RA program. In contrast to the use of multiple immunosuppressive drugs in the transplant program, (tapering doses of glucocorticoids, mycophenolate products and induction therapy with anti-IL-2 monoclonal antibodies), patients with RA received tofacitinib either as monotherapy or in combination with a stable dose of nonbiologic DMARDs that are not potent immunosuppressives, e.g., MTX (weekly dose ≤25 mg). Approximately half of the RA patients were treated with low-dose corticosteroids (daily dose ≤10 mg prednisone equivalent).

Occurrence of Lymphoma in Non-Clinical Studies

At necropsy, tumours considered to be lymphomas were observed in 3 of 8 high dose monkeys in the adult 39-week monkey study. No lymphomas were observed in the 39-week juvenile monkey study at the same doses and at similar exposures as in adult monkeys (0 of 18 monkeys).

Treatment-related lymphomas were observed in 3 of 8 high dose (5 mg/kg BID, 10 mg/kg/day) animals in the 39-week monkey study. Two of the 3 lymphomas from the 39-week monkey study were

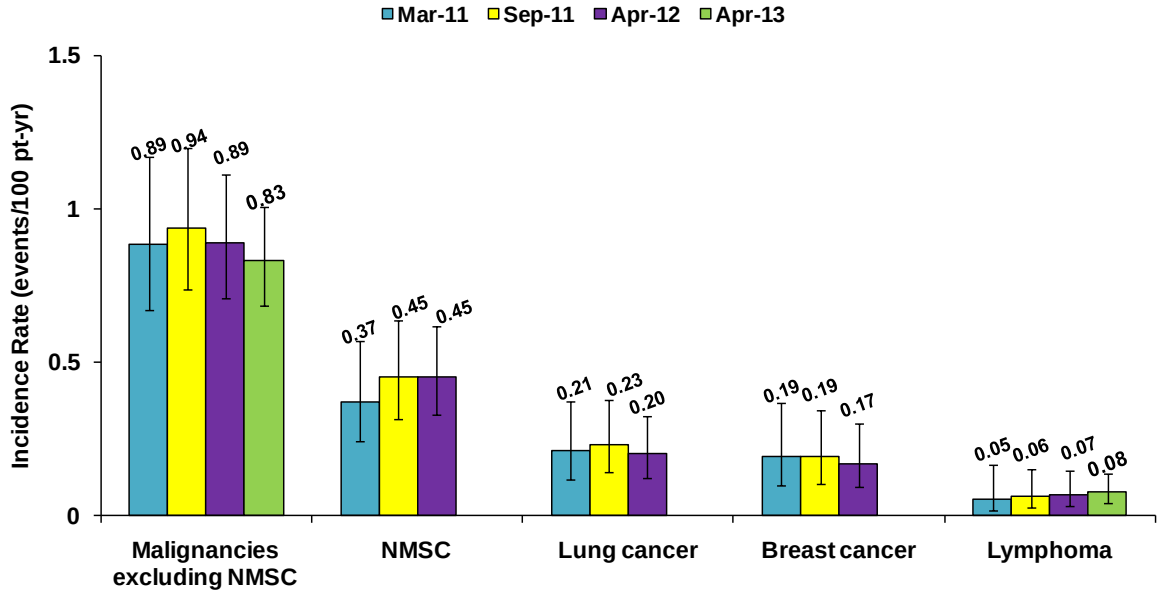
B cell lymphomas and positive for lymphocryptovirus (LCV) by immunohistochemical (EBNA-2) and in situ hybridization (EBER-1) staining. LCV is the term for the Epstein-Barr (EBV)-like gamma herpes virus in cynomolgus monkeys (Carville & Mansfield, 2008). The remaining monkey had a lymphoma in the peri-thymic fat which was determined to be a T cell lymphoma based on immunohistochemical staining.

Chronic immunosuppression in monkeys may be associated with the development of lymphomas. LCV associated B cell lymphomas were not unexpected and were similar to the LCV/EBV positive B cell lymphomas observed with PTLD cases in nonhuman primates (McInnes et al, 2002; Schmidtko et al, 2002) and humans (Swerdlow et al, 2008). Therefore, the LCV-associated lymphomas observed in the 39-week monkey study were considered secondary to immunosuppression.

Malignancy Summary

Rates for all malignancies excluding NMSC, NMSC, lung cancer, and skin cancer were stable across 3 different data cuts (Figure 24).

Figure 24. Cumulative Malignancy Rates across Data Cuts (Events/100 Patient-Year) in Tofacitinib P2P3LTE Studies (All Doses Combined)



NMSC = non melanoma skin cancer; P2P3LTE = Phase 2, Phase 3 and long term extension studies. Includes Studies A3921019, A3921024, A3921025, A3921032, A3921035, A3921039, A3921040, A3921041, A3921044 (2 year), A3921045, A3921046, A3921064, A3921069 (1 year) and A3921109.

In summary, the rates and types of malignancies including lymphoma/LPD reported in the tofacitinib RA program are representative of those described for the RA population in general and in RA patients treated with bDMARDs. As the numbers of patients treated, the number of events reported, and the duration of treatment, have all increased, there has been no increase in the rate of malignancy observed.

An expert statement has been prepared by a rheumatologist in clinical practice in the EU, informed by data from the clinical development of tofacitinib. In this expert statement, the rheumatologist provides his opinion on malignancies.

Malignancy Risk Management Strategy

Risk Minimisation - SmPC

The proposed SmPC addresses the potential risk of malignancy by advising prescribers that tofacitinib may affect host defenses and that malignancies have been observed in patients treated with tofacitinib. For patients with a history of malignancy, prescribers are advised to evaluate the risks and benefits of treatment prior to initiating tofacitinib. Precautions for use related to the risk of lymphoma are specifically communicated in the proposed SmPC.

Risk Minimisation – Educational Plan

The guidance for prescribers in the proposed SmPC will be further communicated through an educational programme directed at both patients and healthcare.

Risk Assessment

Additional studies will be conducted to further characterise the risk of malignancy, including a large RCST with adalimumab as a direct comparator and 3 EU registries. Ongoing central histopathology over-read of malignancy events in clinical studies will aid in risk assessment.

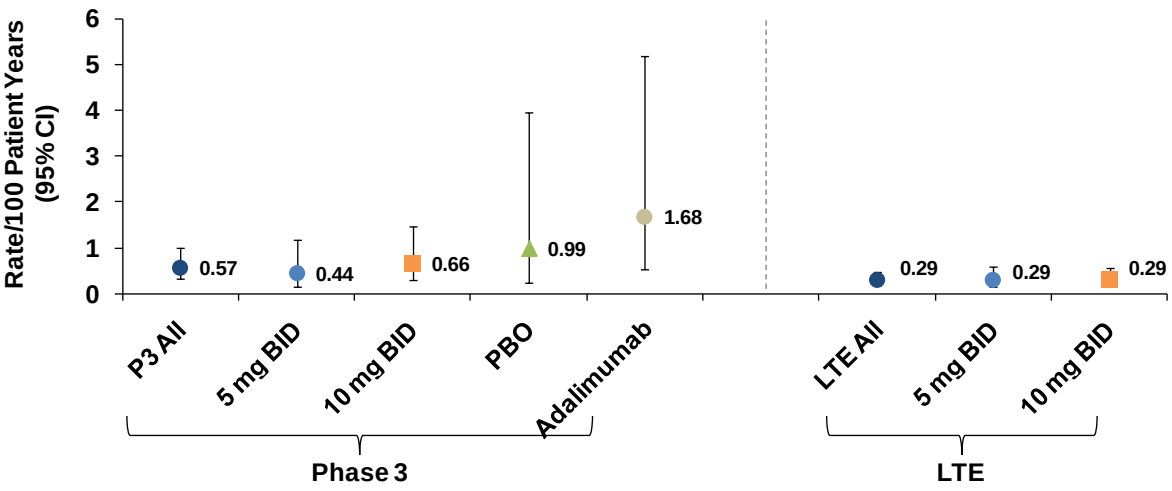
Lipid Increases and Cardiovascular Safety

The Applicant acknowledges that the long-term implications of increases in total cholesterol (TC) and low density lipoprotein cholesterol (LDL-c) in patients treated with tofacitinib are currently unknown even though point estimates of CV event rates (major adverse cardiovascular event [MACE]) on tofacitinib are compared with the placebo and adalimumab dose groups included in the development program. The role of LDL-c in CV disease in RA patients has been discussed extensively in recent years in the medical and scientific literature; data suggest that the role is unclear and in fact may be paradoxical (Myasoedova et al, 2011). Despite similar increases in TC and LDL-c that were reported in RA patients treated with the approved biologic therapy tocilizumab, no increase in CV events has been observed in tocilizumab long-term extension studies (Genovese et al, 2012).

In the tofacitinib development program, CV events and deaths were adjudicated by an independent, blinded committee.

Adjudicated CV event rates from Phase 3 and LTE studies provide evidence that tofacitinib is not associated with an observed increase in CV events (Figure 25).

Figure 25. Incidence Rates of Composite Cardiovascular Events across Dose Groups: Phase 3 and LTE



	All P3	5 mg BID	10 mg BID	PBO	ADA
Pts with events	12	4	6	2	3
Exposure (PY)	2098	903	910	202	179

Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Data as of 19 April 2012

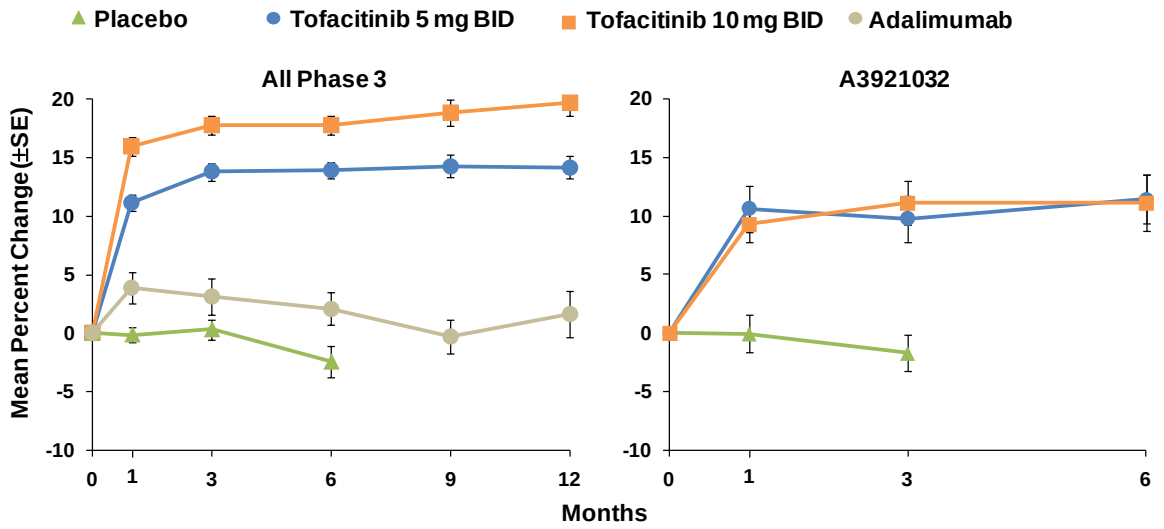
P3 = Phase 3, BID = twice daily, PBO = placebo, LTE = long-term extension, PY = patient-year

Tofacitinib does not appear to be associated with an increase in composite CV events. This conclusion is aligned with the applicant's mechanistic understanding of the lipid changes observed on tofacitinib (see results from Study A3921130 below). Incidence rates of all cause and CV mortality and CV events in the ongoing tofacitinib studies are within the rates expected for the general RA population.

Based on the collective evidence from tofacitinib studies as well as the medical and scientific literature, the Applicant has proposed a risk management strategy that is designed to address what is currently known and unknown about cholesterol levels and CV risk in RA patients.

Dose dependent increases in TC, LDL-c (Figure 26) and high density lipoprotein cholesterol (HDL-c) were observed in patients receiving tofacitinib. These increases occurred within 1 to 3 months of initiation of treatment and remained stable thereafter with continued tofacitinib treatment. Lipid levels return to baseline following discontinuation of tofacitinib (Table 4 and Appendix 8).

Figure 26. Increases in LDL-c with Tofacitinib Treatment



Mean (± SE) Percent Change From Baseline in LDL-c (mg/dL) per Visit - All Phase 3 Studies (Overall 0 to 12 Months) and Study A3921032 (0 to 6 Months)
Data as of 29 March 2011

B

ID = twice daily, LDL-c = low density lipoprotein cholesterol, SE = standard error

Lipid changes in 3rd line RA patients treated with tofacitinib were assessed in Study A3921032; changes were similar to those observed in the overall study population (Figure 26).

The long-term implications of increases in LDL-c in patients treated with tofacitinib are currently unknown. Some RA therapies, such as tofacitinib and tocilizumab, appear to be associated with larger changes in lipid measures than other RA therapies. However, there appears to be a consistent interplay (inverse relationship) between serum lipids and inflammation, such that increases in serum lipids which accompany decreases in inflammation with effective RA therapies may not translate to increased CV risk (Choy et al, 2009 and Myasoedova et al, 2011).

The recently completed exploratory Study A3921130 supports the hypothesis that RA results in abnormal catabolism of lipid moeties, and effective therapy increases lipid levels towards 'normal'. This study and the results are briefly summarised below.

Cholesterol Flux Kinetics Study in RA Patients

Study A3921130: An Exploratory Phase 1, Fixed-Sequence, Open-Label Study to Assess the Effects of CP-690,550 on the Kinetics of Cholesterol Flux Through the High-Density Lipoprotein/Reverse Cholesterol Transport Pathway in Patients With Active Rheumatoid Arthritis

Study A3921130 assessed the effects of tofacitinib on the kinetics of cholesterol flux through the high density lipoprotein/reverse cholesterol transport pathway in patients with active rheumatoid arthritis. A healthy volunteer cohort was included as a baseline control for cholesterol kinetics and lipid levels for comparison to the baseline for RA patients; the RA and control cohorts were matched for race, age, sex and menopausal status and all patients had a body mass index <40 kg/m^2. The findings of this study include the following:

Baseline:

- TC, LDL-c, HDL-c, and apolipoprotein A1 (ApoA1) concentrations were lower in patients with RA compared with matched healthy volunteers

- Markers of HDL function (SAA, HDL SAA, MPO, LCAT activity and mass) were all altered in RA patients vs. healthy volunteers
- Cholesterol ester fractional catabolic rate was significantly different (higher) in RA patients vs. healthy volunteers
- ApoB and ApoA fractional catabolic rate trended higher in RA patients (non-significant)

Treatment with tofacitinib was associated with:

- Increases in TC, LDL-c, HDL-c, and ApoA1 concentrations to levels similar to healthy volunteers
- Changes toward normalization of HDL-associated SAA, LCAT and MPO levels
- Reductions in cholesterol ester fractional catabolic rate to levels of healthy volunteers
- Significantly increased ApoA1 production rate above that of healthy volunteers; no effect on ApoB production

In general, the changes observed in cholesterol kinetics and other lipid parameters following tofacitinib treatment in patients with RA resulted in values approaching the baseline measure of the healthy volunteers.

Two expert statements have been prepared by rheumatologists in clinical practice in the EU, informed by data from the clinical development of tofacitinib. In these expert statements, the rheumatologists provide their opinions on lipid changes and cardiovascular disease.

Cardiovascular Risk Management Strategy

Risk Minimisation - SmPC

The proposed SmPC communicates that tofacitinib is associated with increases in lipid parameters and specific assessment and management recommendations are provided. Hyperlipidaemia and dyslipidaemia are listed as adverse drug reactions (ADRs) and a statement that high cholesterol may be a risk factor for heart disease is included.

Risk Minimisation – Educational Plan

The guidance for prescribers in the proposed SmPC will be further communicated through additional risk minimisation measures and an educational programme directed at both patients and healthcare providers.

Risk Assessment

Lipid and cardiovascular safety will be further asessed in the proposed risk management plan, including adjudication of all CV events occurring in tofacitinib clinical studies by external blinded experts, assessments in 3 EU registries, and a large RCST with adalimumab as a direct comparator. More information about the study is provided in Appendix 4.

Hepatic Safety

Increases in hepatic transaminases were observed in patients treated with tofacitinib; however, increases >3× ULN were uncommon (Table) and occurred with similar frequencies in all treatment groups. As expected, these elevations were more common in patients treated with background DMARDs (primarily MTX). The frequency of transaminase elevations in RA patients treated with tofacitinib is consistent with those reported in RA patients treated with approved biologic therapies (Ghabril et al, 2013).

One patient on 10 mg BID tofacitinib and MTX had possible drug-induced liver injury (DILI). She

experienced asymptomatic transaminase elevations on study and both drugs were discontinued, without normalization of the transaminases. Two to three (2-3) months later she developed jaundice in association with further increases in transaminase levels. The elevated liver tests responded to prednisolone and azathioprine, possibly consistent with autoimmune hepatitis, but DILI cannot be ruled out.

Antirheumatic agents are among commonly used drugs associated with a range of hepatotoxic effects that include autoimmune hepatitis (Aithal, 2011). One case of autoimmune hepatitis was reported in the tocilizumab development program (Genovese et al, 2013); infliximab has been associated with drug induced autoimmune hepatitis (Aithal, 2011), and autoimmune hepatitis has been reported in adalimumab and etanercept treated patients (Ghabril et al, 2013).

Table 117. Incidence (%) of ALT Increases in Phase 3 Studies

	Tofacitinib			Adalimumab
0 to 3 Months	5 mg BID	10 mg BID	Placebo	40 mg q2w
DMARD Studies	**N=968**	**N=962**	**N=554**	**N=204**
ALT				
≥1 x ULN	**248 (26)**	**277 (29)**	**95 (17)**	**48 (24)**
≥3 x ULN	**12 (1.2)**	**12 (1.3)**	**5 (0.9)**	**0**
Monotherapy Study	**N=243**	**N=245**	**N=121**	
ALT				
≥1 x ULN	**35 (14)**	**38 (16)**	**18 (15)**	NA
≥3 x ULN	**1 (0.4)**	**0**	**2 (1.7)**	NA

Data as of 29 March 2011

ALT = alanine aminotransferase; BID = twice daily; DMARD = disease-modifying anti-rheumatic drug; N = number of patients; q2w = every two weeks; ULN = upper limit of normal.

Hepatic safety in patients who had an inadequate response to TNF inhibitors (Study A3921032) was evaluated and found to be consistent with that observed in the overall tofacitinib population. No patients treated with tofacitinib 5 mg BID in the study had transaminase elevations >3× ULN, and there were no patients who met the laboratory criteria for Hy's Law.

Hepatic Risk Management Strategy

Risk Minimisation - SmPC

Information on the frequency of liver enzyme test abnormalities observed in tofacitinib-treated patients is provided in the proposed SmPC and increased hepatic enzymes/transaminases are listed as ADRs. Monitoring of liver enzyme is recommended at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter.Warnings and precautions are provided regarding the use of tofacitinib in patients with ALT or AST >1.5× ULN. In patients with ALT or AST >3× ULN, treatment is not recommended. Prescribers are advised to promptly investigate the causes of liver enzyme elevations to identify potential cases of drug-induced liver injury. If drug-induced injury is suspected, the administration of tofacitinib should be interrupted until this diagnosis has been excluded.

Risk Minimisation – Educational Plan

The guidance for prescribers in the proposed SmPC will be further communicated through additional risk minimisation measures and an educational programme directed at both patients and healthcare

providers.

Risk Assessment

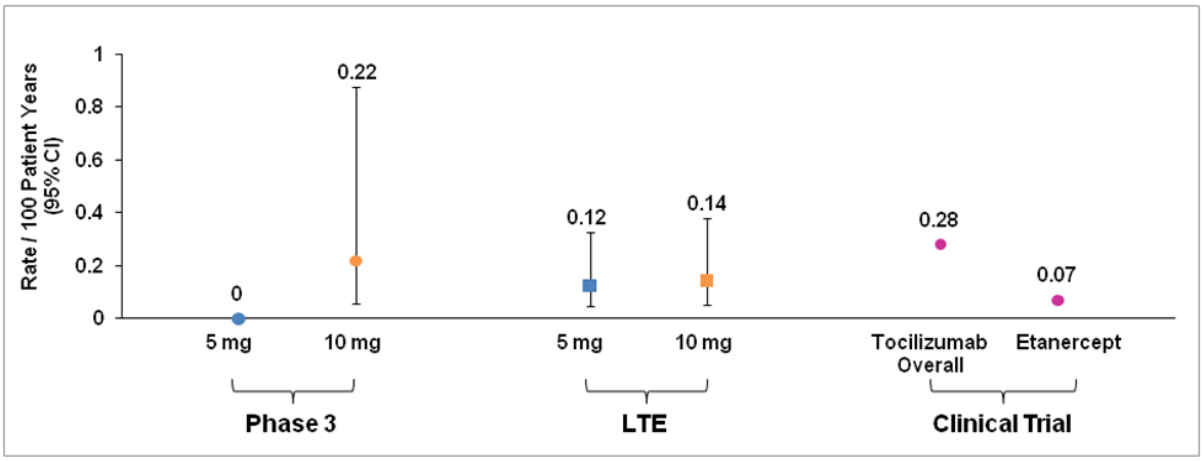
Hepatic safety will be further assessed in the proposed risk management plan, including adjudication of significant hepatic injury events occurring in tofacitinib clinical studies by an external panel of hepatology experts and further assessments in registries.

Gastrointestinal Perforations

Gastrointestinal (GI) perforation is a rare but serious condition that affects patients with RA, most frequently in the lower GI tract. Little is known about the incidence and prevalence of GI perforations in clinical practice among patients with RA. Medications used to treat RA, including NSAIDs, glucocorticoids, and DMARDs, have all been associated with increased risk of GI perforation (Curtis et al, 2012).

Ten tofacitinib treated patients in the Phase 3 and LTE studies experienced a GI perforation; the incidence rates are similar to those reported for TNF inhibitor therapy (Figure 27). All patients with GI perforations had associated risk factors including concomitant use of NSAIDs and/or glucocorticoids (Curtis et al, 2012). Several of these events occurred in the setting of diverticulitis, also identified as an associated risk factor.

Figure 27. Gastrointestinal Perforation Rates, Overall Tofacitinib Program



	5 mg BID	10 mg BID	5 mg BID	10 mg BID
Patients with events	0	2	4	4
Patient years	904	910	3243	2791

Bars indicate 95% Confidence Intervals (none where estimate is zero)
Dots for other drugs represent point estimates found in different published sources
Tocilizumab estimate from Van Vollenhoven et al, 2009
Data as of 19 April 2012

Bars indicate 95% Confidence intervals (none where estimate is zero); Dots for other drugs represent point estimates found in published sources; tocilizumab estimate from Van Vollenhoven et al, 2009; etanercept estimate from Combe et al, 2010; 5 mg or 10 mg refers to tofacitinib; Data as of 19 April 2012

There were no GI perforations reported in Study A3921032, nor were there GI perforations reported in other Phase 3 and LTE studies in 3rd line patients for the proposed 5 mg BID dose.

An expert statement has been prepared by a rheumatologist in clinical practice in the EU, informed by data from the clinical development of tofacitinib. In this expert statement, the rheumatologist provides his opinion on gastrointestinal perforations.

Gastrointestinal Perforation Risk Management Strategy

Risk Minimisation - SmPC

GI perforations observed in tofacitinib-treated patients are described in the proposed SmPC including specific information on potential risk factors, patients in whom tofacitinib should be used with caution (e.g., patients with diverticulitis), and symptoms which should alert patients and healthcare providers to the possibility of a GI perforation.

Risk Minimisation – Educational Plan

The guidance for prescribers in the proposed SmPC will be further communicated through additional risk minimisation measures and an educational programme directed at both patients and healthcare providers.

Risk Assessment

The Applicant is committed to continued evaluation of GI perforations in registry studies as well as ongoing and future clinical studies.

Additional expert consultation – Report from the ad-hoc expert group meeting held on 15 July 2013

Following a request from the applicant at the time of the re-examination, the CHMP convened an ad hoc expert group meeting inviting the experts, including patient representative, to provide their views on the questions posed by the CHMP, taking into account the applicant's response to the grounds for refusal.

1) If risk-benefit is ultimately determined to be positive, what would be the most appropriate place for this treatment option, contrasting the potential high risks of opportunistic infections, cardiovascular events, hepatotoxicity and gastrointestinal safety concerns with the safety profiles for other DMARDs?

The group had a split opinion on this question whereby all experts recognised the limitations of the evidence regarding the lack of a robust effect on radiographic progression of disease for 5 mg bid. Half of the experts were of the opinion that the prevention of structural damage had not been adequately demonstrated by the applicant for the 5 mg dose in the proposed TNF failure population. In view of this lower efficacy and taking into account the safety profile of the product, these experts took the view that tofacitinib has no place in the therapeutic armamentarium considering the availability of alternative medicinal products such as abatacept, tocilizumab and rituximab which have robustly demonstrated beneficial effects on structural damage with a better characterised safety profile. A "4th line" use only after these alternative treatments have failed was not a sensible option in clinical practice. It was also raised that patients using tofacitinib as 3rd line therapy will be at higher risk of infections as shown by the emergence of tuberculosis in spite of previous screening.

The other experts were either of the opinion that sufficient data are available to support the prevention of structural damage claim, or that, considering the 3rd line therapy proposed by the applicant, it is difficult to expect remission in this patient population and that low disease activity is an important parameter for which tofacitinib demonstrated a similar effect to rituximab and abatacept. These experts did see the safety profile of tofacitinib as being similar to tocilizumab and therefore supported the proposed use of the product in patients who have had an inadequate response with at least one biological DMARD.

From a patient perspective, it was highlighted that the oral formulation is an added value if it is as effective as the other available treatments. However it was emphasised that the formulation of the product alone should not be the main criteria for approving a medicine and that the parameters for licensing a product with a new mechanism of action should be seen against the proven effects of therapies already available. The lower efficacy is therefore of concern.

Overall, the experts unanimously agreed that the data available did not demonstrate that tofacitinib can be considered to be on par with TNF inhibitors given the uncertainty and magnitude of the beneficial effects on radiographic progression and its adverse effect profile.

2) Because of the dose-dependent safety risks, the dose is limited to 5 mg bid. However, the prevention of structural damage was not robustly shown for the low dose, in contrast to the 10 mg dose.

a) Would a drug that is shown effective in reducing signs and symptoms in a manner similar to adalimumab (regarding DAS28/ACR scores), but with greater uncertainty in terms of its effect on prevention of structural damage, still be considered as a useful treatment option for the proposed target population (patients intolerant to previous therapy with at least one biological DMARD)?

There were different opinions raised by the experts, in line with the response to question 1. Half of the experts expressed the view that there is no robust structural data to support efficacy in this population.

They noted that head to head comparisons with non-TNF inhibitors biological DMARDs such as tocilizumab and abatacept were not available. Also it was raised that this population was only supported through post-hoc analyses. Therefore as the prevention of structural damage was not demonstrated, tofacitinib cannot be considered as a useful treatment option for the proposed target population.

The other experts expressed the view that the tofacitinib's ACR 70 data as well as DAS28 data were convincing to demonstrate that tofacitinib is not less effective than a biological DMARD. Therefore, taken together with the available data on structural damage, tofacitinib could be considered as a useful treatment option in the proposed target population.

b) Given the safety data, should dose increments be allowed at insufficient DAS28 response, e.g. when there are no other alternative treatments available?

The experts unanimously agreed that dose increments should not be recommended.

3) The safety profile of tofacitinib includes a broad range of adverse events, regarding opportunistic and/or serious infections, increments of lipids/ liver enzymes/creatinine kinase, and perforations of lower GI tract. Several safety measures are proposed, such as routine monitoring of lymphocytes, transaminases, and lipids, and excluding patients with diverticulitis.

a) What kind of additional measures/strategies to the proposed ones could be considered, including, but not limited to, possible screening and/or monitoring measures, as well as prophylactic and/or pre-emptive therapies? Which aspects of safety management with other DMARDs, such as TNF-I and tocilizumab, should be implemented for tofacitinib as well?

Overall, the group was of the view that the measures proposed by the applicant for the safety management were adequate; it was suggested that they should be similar to the ones for tocilizumab. In addition though, the experts recommended the use of an interferon-gamma release assay to screen for latent tuberculosis rather than tuberculine skin testing due to the poor sensitivity and specificity of the latter in an immunosuppressed population.

b) Would it be useful to add: routine monitoring of oral candiasis, monitoring and excluding patients with NMSC (non-melanoma skin carcinoma), and providing varicella prophylaxis?

Regarding monitoring of oral candidiasis, the experts considered that regular mouth inspection could be performed in an outpatient rheumatology setting but that it would not be effective in picking up oesophageal candidiasis. Appropriate information regarding this risk should be included in the product information leaflet.

The experts agreed that inclusion of NMSC as a warning in the label is appropriate.

Regarding the proposal for varicella prophylaxis, the experts expressed concerns given that this is a live vaccine and the proposed indication is for use in a 3rd line immunosuppressed population. There is a lack of data on use of a live vaccine in these immunosuppressed patients, which may potentially be unsafe. The experts agreed that physicians and patients should be made aware in the product information of the risks associated with the use of live vaccines in immunosuppressed patients and clear guidance would need to be provided. The experts also recommended that additional data on the use of live vaccines in tofacitinib treated patients should be gathered.

4) Overall the non-clinical studies suggest that tofacitinib is a first in class selective T-cell immunosuppressant which inhibits proliferation and differentiation of the NK cells, CD8 memory cells and also impairs the delayed-type hypersensitivity (DTH) reaction. Some pharmacodynamic effects were found to be irreversible. The dose-response effect for these findings is unclear. Despite these non-clinical findings, T-cell subset data was not systematically collected and immunophenotyping was not conducted in the clinical development programme hence quantitative/qualitative conclusions are limited. Decreases in the NK cell, CD8 and CD4 cell populations were however noted and the spectrum of opportunistic infections were suggestive of impaired cell mediated immunity.

a) The applicant states that changes in lymphocyte subset counts in rats/monkeys are not predictive of effects in humans due to qualitative and quantitative differences and that conclusions should be based on clinical data, however the data generated in the clinical development programme with regards to impact on immune function are limited. The only clinical evidence of functional impairment is derived from vaccine sub-studies, in which a reduced response was observed. No further functional data, for example the impact on the DTH response or NK cell assays at the proposed level of exposure have been presented. Is the presented vaccine data considered sufficient to characterise the functional impairment caused by tofacitinib?

The experts observed that the data on pneumoccocal and influenza vaccines presented, showed some impairment of vaccine responsiveness but that patients on tofacitinib are still capable of mounting an antibody response showing that the immune response of treated patients is, at least, partially preserved.

However it was acknowledged that data originating from studies performed with live vaccines would have been more helpful to support the recommendation for immunisation with varicella vaccine.

b) Is it useful to request further functional data using ex-vivo assays (at a minimum for T/B/NK/macrophage function) and provide evidence of reversibility of PD effect either from humans or appropriate animal species for example NK cell assays or host resistance assays to better characterise the functional impairment caused by tofacitinib, at the proposed exposure level? Would this help inform the benefit:risk, the RMP and the clinical management of the identified safety risks in relation to infections?

One expert was of the opinion that, as tofacitinib targets T cells, DTH response data would have been helpful to characterise the functional impairment caused by tofacitinib. Some experts were of the view that DTH response is not a good predictor of functional impairment in an immunosuppressed population, who are likely to be anergic, and that functional NK cell and macrophage assays are not easy to perform.

The experts agreed that it was not feasible or practicable to perform functional assays on T cells, NK cells and macrophages in routine clinical practice. Regarding B cell function, the experts recommended measuring serum immunoglobulins before the start of treatment with tofacitinib.

The experts supported the proposal of the applicant to conduct a post marketing surveillance study on the effect of tofacitinib on lymphocyte subsets.

5) Tofacitinib affects cellular immunity, and reduce CD4/8 and NK cells

a) Can the results about the level of reversibility of immunological pharmacodynamic effects be considered as shown and acceptable in the clinical management in the proposed 3rd line population?

The experts expressed the view that the level of reversibility of the immunological pharmacodynamic effects as shown was acceptable in the clinical management of patients receiving tofacitinib as a proposed 3rd line medication.

Some experts were also of the view that the fall in CD4/CD8 cells is minimal. The fall in NK cell is a direct reflection of the way tofacitinib acts (impact on IL-15) and is expected. Whether measuring NK cell numbers beforehand would be a predictor of risk of opportunistic infections is unknown.

One expert mentioned that a thorough immune investigation including NK cell in the beginning of treatment is very important because the mode of action of tofacitinib is different from the already approved products.

b) Total lymphocyte count (TLC) partially explained the risk of serious and/or opportunistic infections, and it is suggested to monitor TLC in patients. Could TLC alone be considered as a sufficient monitoring instrument, considering that CD4/8/NK cells contribute to a small part of the TLC? Would monitoring of CD4/8/NK cells, or other subsets of lymphocytes reduced by JAK1-3 inhibition, feasible in clinical practice?

The experts expressed the view that total lymphocyte count is a reliable monitoring instrument and that lymphocyte subset monitoring does not add value beyond total lymphocyte count.

The experts also agreed that tofacitinib should be contraindicated in patients with a lymphocyte count less than 500 cells/mm^3 and recommended a monitoring of the TLC on a monthly basis as long as the value is beyond 1000 cells/mm^3, with a greater frequency below 750 cells/mm^3. From a patient perspective it was re-emphasised that it should be clearly communicated to the patients in the in the package leaflet that doctors will perform blood tests before and during treatment with tofacitinib, to determine the level of the white blood cell count.

PRAC Advice

Based on the PRAC review of the Risk Management Plan for Xeljanz (version dated 22 May 2013), the PRAC considered by consensus that the risk management system for tofacitinib is not acceptable.

PRAC advice on the specific CHMP questions:

1) Are the risk minimisation measures as proposed for the main safety issues appropriate? Main safety issues are serious (opportunistic) infections, haematologic disorders (leucopenia, lymphopenia, anaemia), cardiovascular disorders, lymphoma and gastro-intestinal perforations. If not, what are the essential alternative measures needed?

The PRAC advised that the risk minimisation measures proposed by the Applicant would not be sufficient to characterise all the risks associated with the use of tofacitinib. Further risk minimisation measures would be required to minimise the risks of infections and lymphoma.

Oro-oesophageal candida is a main infection among the reported opportunistic infections. To minimise the risk of this infection, regular mouth inspections should be performed. This action should be included in the SmPC in section 4.4 as a precautionary measure and also reflected in the RMP.

The risk of lymphoma is of particular concern due to the high incidence rates observed of such events in patients treated with tofacitinib and the Applicant should elaborate on possibilities for early detection and the way these might be helpful to mitigate the risk.

Considering the increased background cardiovascular risk of patients with rheumatoid arthritis and the cardiovascular concerns associated with the use of tofactinib. Sufficient data are lacking, as patients at low risk were included in the trials. The applicant should consider to have a cardiovascular risk profile of patients who are at high risk for cardiovascular events, e.g. because of lipid elevations (incl hypercholesterolaemia), obesity, hypertension and other cardiovascular disorders. These patients should be monitored more stringently than patients without this risk profile.

The PRAC was not able to identify suitable practical measures other than the ones currently proposed by the Applicant for the risk of gastric perforation and opportunistic infections. Of particular concern was the risk of opportunistic infections in particular which was identified as being especially challenging to manage with the proposed measures.

Varicella vaccination or prophylaxis with immune globulins might be an interesting option to mitigate the risk. However, the vaccines are not generally available in Europe, and therefore this measure is not considered ultimately feasible.

The PRAC also considers that other important risks not identified by the Applicant need to be addressed in the RMP and these include the risks of non-melanoma skin cancers (NMSC) and off-label use in doses higher than the one recommend in the SmPC and in indications other than the proposed one.

For NMSC it is recommended to exclude patients with newly diagnosed NMSC from treatment, and to include a monitoring advice for NMSC as a risk minimisation measure in the SmPC and RMP.

The PRAC considered that limiting off-label use would be particularly challenging and special consideration should be given in suitable risk minimisation measures to minimise this risk.

The PRAC noted that extensive warnings and a very detailed educational programme for healthcare professionals was being proposed to minimise the known risks of tofacitinib and it was recognised that there would be difficulties in ensuring compliance with all of these measures.

2. Does the PRAC agree with the effectiveness assessment of the proposed risk minimisation measures, as there are: survey's to evaluate the knowledge and understanding of the Educational Material? If not, which additional tools should be included?

The PRAC considered that the proposed surveys to assess the effectiveness of the proposed risk minimisation was inadequate and would only test the patients and health care professionals on the contents of the SmPC and educational material. Further questions in these surveys would be required to gain some information on the compliance with the risk minimisation measures. Furthermore the Applicant should consider specific studies, such as a drug utilisation study, to ensure adherence to the proposed risk minimisation measures.

Additional information provided by the Applicant

During the Oral Explanation on 22 July 2013, the Applicant proposed to further revise the indication as follows:

Tofacitinib, in combination with methotrexate (MTX), is indicated for treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an inadequate response or are intolerant to previous therapy with at least one biological DMARD.

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

Tofacitinib has been shown to improve physical function.

The applicant also proposed various risk management measures.

Overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant and considered the views of the PRAC (PRAC meeting 8-11 July 2013) and the advisory expert group held on 15 July 2013.

CHMP position on ground 1

The short term effects on structural damage (placebo controlled study 1044) were difficult to interpret, since effect estimates lean heavily on the use of linear extrapolation of progression rate from 3 months to 6 months for a large part of the placebo group, for both the primary analysis (change in mTSS) and responder analysis ("no radiographic progression at month 6"). Numerically, it can be seen that progression is slowed down for placebo patients after switching to tofacitinib, which supports its ability to slow down progression, but the magnitude of the effect is uncertain. The effect also appears to be roughly in line to historical data of biological DMARDs, however, these comparisons should be interpreted with care as there may be differences in the prognostic factors between study populations. Moreover, no definitive conclusions could be drawn from the subgroup analysis of TNF-IR patients, as tofacitinib did not differentiate from placebo to a statistically significant degree.

The results for the proposed 5 mg dose are not as robust as for the 10 mg dose. Statistical significance was neither achieved in some primary and sensitivity analyses, nor in the subgroup of interest (i.e. the proposed target population of biological DMARD irresponsive patients). More importantly, it is also noted that the 5 mg dose is overall less optimal in preventing structural damage than the 10 mg dose, including in the proposed target population of patients irresponsive to biological DMARDs. This on its own is the main reason why the effect is not considered robust or relevant for the 5 mg dose, and that a specific indication is not justified.

The CHMP concluded that the prevention of joint damage is the ultimate goal in treatment of RA in the first- and second-line indication. At the proposed, 5mg dose BID level, prevention of structural damage has still not been robustly shown. During the Oral Explanation on 22 July 2013, the Applicant proposed to withdraw the claim regarding the reduction of structural damage from the indication. The CHMP however considered that the reduction of symptoms is also an important treatment goal for a disease-modifying agent and the absence of a demonstration of effect on structural damage at the proposed dose, relevant to the proposed target population, was a considerable uncertainty in the dossier.

CHMP position on ground 2

The applicant argued that relevant information from the toxicological program was followed up in the clinical development program, but the species differences between rodents, monkeys and humans prevented from precise understanding. Observations in monkeys and other animal species could not be reproduced in humans. It is known from the literature on immunosuppressive compounds that animal data pointed to effects on the immune system should be used as a signal to be followed up, although the translatability is not always easy, and extrapolation from animals to humans should be based more on general principles.

Pharmacodynamic (PD) data and lymphocyte monitoring

Tofacitinib affects cellular immunity in RA patients, as could be expected based on the fact that tofacitinib inhibits several interleukins known to be involved in the proliferation of lymphoid cells (e.g.IL7, IL21), and as confirmed in both pre-clinical and clinical studies. In the limited data available, only median rate of decline from baseline are presented, and it is not clear how many subjects actually had CD4/8 levels below a critical level. The spectrum of observed infections associated with the lymphopaenias could have been predicted from the mechanism of action of tofacitinib and the consequential severe impairment of cell-mediated immunity. The applicant has not presented adequate evidence of reversibility of this pharmacodynamic effect on the immune system.

The CHMP was of the opinion that the applicant did not sufficiently investigate in the main clinical development programme to what extent tofacitinib influences cellular immunity at the proposed dose level, and how this relates to the clinical efficacy and safety. This is a drawback, as monitoring of the CD4/8 cells or other lymphocyte subsets might be helpful in controlling infection risk further. Furthermore, it has not been evaluated how the PD effects of tofacitinib on the cellular immune system relate to other DMARDs, like MTX and TNF-I. This would have been helpful in the assessment of the relative risks, and understanding of the mechanism of action.

The applicant claimed that the PD effect of tofacitinib is likely shorter than for biological DMARDs, as tofacitinib has a short elimination half-life (3 hours) compared to biological DMARDs (several weeks). However, there are insufficient data on the “PD half-life” (i.e. the recovery of specific lymphocytes after treatment interruption).

The applicant proposed to monitor total lymphocyte count (TLC) routinely in patients, as TLC contributed to the risk of opportunistic and/or serious infections. However, TLC only partially explained the risk serious and/or opportunistic infections. TLC may be a too crude measure, considering that subsets of lymphocytes of interest (CD4/8) contribute to a small percentage of the overall Total Lymphocyte Count. However, the absence of a thorough investigation during the clinical development programme means that the characterisation of the risk is not sufficent and that therefore a monitoring strategy adequate to manage the risk in clinical practice cannot be determined.

Clinical safety data of infections

The main question was whether the specific effect of tofacitinib on the cellular immunity, increases the risk of infections, or result in a different type of infections, in relation to alternative DMARDs treatment options.

The incidence of herpes zoster was 1.6 fold higher as compared to TNF-I adalimumab in direct comparison, and twice as high than MTX in the monotherapy study in naïve patients. The applicant stated that the observed incidence of herpes zoster is overall higher than reported for the DMADS in the literature.

In a direct head-to-head comparison, the incidences of serious infections requiring hospitalisation were as nearly as twice as high for tofacitinib than for TNF-I adalimumab. In contrast, the serious infection incidence rates of the tofacitinib trials were in line with other bDMARDs, including adalimumab, in a

meta-analysis. This analysis was conducted using data from a number of different clinical trials, including different patient populations and assessments, precluding a fully reliable inference. Moreover, it is noted that in the main tofacitinib trials, patients at low risk of infections were selected, and that in the target population of heavily pre-treated patients, the risk of infections may be higher.

In the literature, invasive fungal infections, TB, Cryptococcus, and disseminated Herpes Zoster are reported as well. It is, however, difficult to compare rates between studies, as no standard definition of opportunistic infections has been applied in the literature. In general, with an incidence of 0.8% in the pooled dataset of subject treated with 5 mg dose, opportunistic infections are considered as an important risk of tofacitinib.

Risk management of infections

The Applicant proposed the following measures to minimise the risk: (a) only the low 5mg dose is allowed as risk increased with the 10 mg dose, (b) total lymphocyte counts has to be monitored and treatment should be interrupted at low counts (<500/mm^3), and (c) all patients have to be screened for TB and hepatitis prior to treatment. Furthermore, warnings are included in the SmPC for established risk factors of infections such as high age, diabetes comorbidity and steroid use.These measures were considered appropriate by the CHMP although not sufficient to resolve the uncertainties regarding the broad impact of tofacitinib in the humoral and cellular immune system.

The CHMP concluded that there is a high degree of uncertainty related to the high risk of infections as patients treated with tofacitinib developed serious and fatal opportunistic infections and the spectrum of these disorders is indicative of impaired cell-mediated immune function. The PD effects of tofacitinib on cellular immunity as observed in preclinical studies has not been adequately followed up in the clinical study program and therefore not been sufficiently answered by the applicant. In addition, opportunistic and serious infections were reported for tofacitinib. The risk of infections is expected to be even higher in the proposed target population of advanced patients pre-treated with other immune-modulating DMARDs, including a biological one. Some phase-3 studies included patients who failed biological DMARDS, and apparently the point estimates of infection risks were similar as reported for the overall study population. But the dataset is considered overall too small to draw firm conclusions regarding the target population of patients failing at multiple DMARDs. There remain too many uncertainties regarding safety in this more vulnerable population to allow marketing authorisation at this stage.

Moreover, from the data presented, it remained unclear whether patients that experience a drop of CD4/8 or other lymphocytes subsets due to tofacitinib treatment, recover once treatment is withdrawn. The applicant has insufficiently justified why the uncertainties that are introduced by not following the recommendations for performing functional immune assays according to ICH-S8 guidance document can be acceptable. Finally reversibility of pharmacodynamic effect was not considered to be adequately demonstrated.

CHMP position on ground 3

Solid tumours

The overall malignancy rate (excluding NMSC) for these patients was 0.83 (95% CI: 0.685, 1.004) (data cut April 12013), which is slightly less, but consistent with, the overall rate of malignancy in previous data cuts. This was a matter of concern for the CHMP, as data were presented at a cut-off at month 36. Though the compound was not mutagenic in the preclinical studies, it is not excluded that reduction of NK cells by tofacitinib might contribute to the risk. At longer follow-up from 36 months, the rates decreased again till 0.3-0.6 per 100 PY, although it is difficult to draw conclusions from the small selected population treated longer than 36 months. The overall incidences throughout the monitoring period are also in line with what

is reported for other DMARDs. No increasing trend was observed for most common malignancies during 2 year follow-up.

The CHMP concluded, based on the data available, that tofacitinib is unlikely to have a higher risk of solid tumours as compared to other biological DMARDs. However there is remaining uncertainty and longer follow-up data are needed to further establish this.

Lymphoma

The risk of lymphoma has been established in monkeys and in transplant patients, at doses exceeding the maintenance dose in RA. At low doses used in the RA trials the risk was similar to comparator adalimumab. However, the data presented do not exclude a cumulative risk at long term use of the low dose, as the incidence rate nearly doubled (from 0.05 to 0.08 per 100PY) in 2 year follow-up phase. Although with the narrowing of the confidence interval may be an early signal of stabilizing, it is premature to rule out a further increasing trend. The reported incidence after 2 years was within the range as reported for TNF-I and other bDMARDs like abatacept and tocilizumab (0.06-0.14 per 100 PY). RA patients are known to be a population at risk of lymphoma, independent of treatment. However, further follow-up vigilance is required to further establish this.

Thus far, the long-term follow-up data from tofacitinib did not show an increased risk compared to other RA patients and DMARD therapies. However there is remaining uncertainty and further confirmation is needed, especially in the vulnerable target population of patients pre-treated with multiple immune-modulating DMARDs.

Other AEs (Lipids, cardiovascular risks, liver enzymes and GI perforation)

The impact of the lipid changes at the due of tofacitinib on the risk of cardiovascular incidents is unclear. The cholesterol flux kinetics study showed that that HDL and LDL cholesterol increased from baseline after the introduction of tofacitinib in patients, but that their baseline levels were lower than healthy volunteers, and that their lipid levels increased to the reference healthy volunteer population. Also in other studies, it has been confirmed that cholesterol levels are relatively low in highly active disease.

In the tofacitinib clinical trials, no increased risk of cardiovascular events was observed for tofacitinib compared to adalimumab and reference data from the general RA population. However, this should be interpreted with care as a selected population at low risk was included in the trials. Further monitoring regarding the risk of CV events in real-life treatment setting would therefore be required, especially considering that RA patients are a population at risk for CV incidents, and obesities and diabetes are more common in RA patients. Moreover, hypertension was more commonly reported for tofacitinib as compared to placebo.

In general, the safety profile of tofacitinib is considered unfavourable, considering the lipid changes, increments of transaminases and potential hepato-toxicity, and lower tract gastro-intestinal perforations, which are all less commonly reported for adalimumab in the direct comparison.

Conclusion on safety

The CHMP concluded that there are major uncertainties regarding the risk of opportunistic and/or serious infections, malignancies, lymphoma, gastro-intestinal perforations, hepatic enzymes elevations/drug-induced liver injury and lipids and cardiovascular risks in the tofacitinib third-line target population. 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 for the claimed target population. Based on these uncertainties, the CHMP considered the safety profile to be of major concern and that the risks were manageable in clinical practice.

During this re-examination procedure the applicant proposed various risk management measures. However the CHMP was not reassured that that these risk minimisation measures resolve the uncertainties pertaining to the safety of the product

Recommendations following re-examination

Based on the arguments of the applicant and all the supporting data on quality, safety and efficacy, for Xeljanz in the proposed indication:

> Tofacitinib, in combination with methotrexate (MTX), is indicated for treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an inadequate response or are intolerant to previous therapy with at least one biological DMARD.
>
> Tofacitinib can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.
>
> Tofacitinib has been shown to improve physical function.

the CHMP re-examined its initial opinion and in its final opinion concluded by majority decision the refusal of the granting of the marketing authorisation for Xeljanz. The CHMP considers that:

Whereas

- 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.
- 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.
- 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 in the proposed target population.

The CHMP remains of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the safety and efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated.

Therefore, the CHMP has recommended the refusal of the granting of the marketing authorisation for Xeljanz.

Divergent positions to the majority recommendation are appended to this report.

Divergent Position

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the refusal of the granting of a Marketing Authorisation for Xeljanz as third-line treatment option in RA. The reasons for divergent opinion were as follows:

Tofacitinib represents a drug from a new class in RA treatment. Particularly, patients not responding sufficiently to standard care may benefit of alternative options targeting other pathways. In contrast to recent developments in RA treatment of biological DMARDs, the product is an oral formulation, which may be an advantage for certain patients.

Efficacy of both tofacitinib and other third-line treatment options were qualitatively and quantitatively fairly alike when evaluating ACR50, ACR70 and DAS28 scores in patients. A rapid reduction of symptoms and a sustained control of disease activity to a low level - as confirmed in Phase III trials in the target population- is an important and realistic therapeutic goal in patients who failed to first- and second-line treatment options. The lack of hard evidence of prevention of structural damage in patients failing to other DMARDs is secondary in this perspective.

Earlier concerns regarding recovery from the PD immune response, is considered sufficiently addressed based on the Phase II data provided from about 500 subjects. Compared to biological DMARDs, especially products targeting B-cells, both the PK and PD half-life is considerable shorter. The observed risk of serious and opportunistic infections is important and should by no means be underestimated. However, it is not considered that the infections risks would be significant less for the other alternative treatment options available for patients failing on prior biological DMARDs. Taking regional background risk into account, the risk of tuberculosis and other opportunistic infections like PCP (predominant in Asia), was similar as reported for TNF-inhibitors. The risk of herpes zoster was however overall higher than TNF-inhibitors or other biological DMARDs. Therefore tofacitinib is not considered on par, and should be positioned after bDMARD, as proposed in the indication. As recommended by the ad-hoc expert group meeting (July 15, 2013), it is proposed to further evaluate the possibility of varicella vaccination.

The possible risk of malignancies and dose-dependent risk of EBV-related lymphoproliferative disorders or lymphoma is of serious concern. However, the current dataset of approximately 13,000 patient-years does not suggest an increased risk as compared to other DMARDs, nor an increasing trend at continued use of the 5 mg dose for 3 years follow-up. Considering the severity but also rarity of these events, these should be further closely monitored in large-scaled databases, such as post-authorisation studies and registries, as already proposed by the PRAC and MAA. The same applies for other identified and potential risks, like increment of lipids and transaminases, and GI perforations. These risks are important and strict monitoring is needed, however, these risks are not unique for tofacitinib, and considered manageable by trained rheumatologists.

In summary, the safety data set in the proposed target population failing to at least one biological DMARD, is small. However, by proposing a restricted population with a high medical need, a better pre-cautionary balance with the uncertainties related to the efficacy and safety profile of tofacitinib has been achieved. It is considered that the former grounds of refusal have been sufficiently addressed by the data and Risk minimisation measures/Risk Management Plan. The benefit-risk balance in a restricted indication leaving out the structural damage claim is positive, provided that the recommendations of the PRAC and ad-hoc expert group meeting regarding the Risk Management Plan will be implemented.

London, 25 July 2013

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John-Joseph Borg (Malta)

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Kristina Dunder (Sweden)

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Concepcion Prieto Yerro (Spain)

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Jacqueline Genoux-Hames (Luxembourg)

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Jens Heisterberg (Denmark)

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Stanislav Primožič (Slovenia)

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